Role of dystrophin and utrophin for assembly and function of the dystrophin glycoprotein complex in non-muscle tissue

Haenggi, T ; Fritschy, J -M

Abstract: The dystrophin glycoprotein complex (DGC) is a multimeric protein assembly associated with either the X-linked cytoskeletal protein dystrophin or its autosomal homologue utrophin. In striated muscle cells, the DGC links the extracellular matrix to the actin cytoskeleton and mediates three major functions: structural stability of the plasma membrane, ion homeostasis, and transmembrane signaling. Mutations affecting the DGC underlie major forms of congenital muscle dystrophies. The DGC is prominent also in the central and peripheral nervous system and in tissues with a secretory function or which form barriers between functional compartments, such as the blood-brain barrier, choroid plexus, or kidney. A considerable molecular heterogeneity arises from cell-specific expression of its constituent proteins, notably short C-terminal isoforms of dystrophin. Experimentally, the generation of mice carrying targeted gene deletions affecting the DGC has clarified the interdependence of DGC proteins for assembly of the complex and revealed its importance for brain development and regulation of the 'milieu intérieur. Here, we focus on recent studies of the DGC in brain, blood-brain barrier and choroid plexus, retina, and kidney and discuss the role of dystrophin isoforms and utrophin for assembly of the complex in these tissues

DOI: https://doi.org/10.1007/s00018-005-5461-0

Cell. Mol. Life Sci. 63 (2006) 1614–1631
1420-682X/06/141614-18
DOI 10.1007/s00018-005-5461-0

Cellular and Molecular Life Sciences

Review

Role of dystrophin and utrophin for assembly and function of the dystrophin glycoprotein complex in non-muscle tissue

T. Haenggi[+] and J.-M. Fritschy*

Institute of Pharmacology and Toxicology, University of Zurich, Winterthurerstrasse 190, 8057 Zürich (Switzerland), Fax +41 44 635 6874, e-mail: fritschy@pharma.unizh.ch

Received 4 October 2005; received after revision 14 March 2006; accepted 5 April 2006
Online First 15 May 2006

Abstract. The dystrophin glycoprotein complex (DGC) is a multimeric protein assembly associated with either the X-linked cytoskeletal protein dystrophin or its autosomal homologue utrophin. In striated muscle cells, the DGC links the extracellular matrix to the actin cytoskeleton and mediates three major functions: structural stability of the plasma membrane, ion homeostasis, and transmembrane signaling. Mutations affecting the DGC underlie major forms of congenital muscle dystrophies. The DGC is prominent also in the central and peripheral nervous system and in tissues with a secretory function or which form barriers between functional compartments, such as the blood-brain barrier, choroid plexus, or kidney. A considerable molecular heterogeneity arises from cell-specific expression of its constituent proteins, notably short C-terminal isoforms of dystrophin. Experimentally, the generation of mice carrying targeted gene deletions affecting the DGC has clarified the interdependence of DGC proteins for assembly of the complex and revealed its importance for brain development and regulation of the 'milieu intérieur'. Here, we focus on recent studies of the DGC in brain, blood-brain barrier and choroid plexus, retina, and kidney and discuss the role of dystrophin isoforms and utrophin for assembly of the complex in these tissues.

Keywords. Blood-brain barrier, choroid plexus, dystrophin, Dp71, epithelial cell, endothelial cell, homeostasis, kidney, retina, targeted gene deletion, transmembrane signaling, utrophin.

Introduction

The dystrophin glycoprotein complex (DGC) comprises five classes of proteins (dystroglycans, syntrophins, dystrobrevins, sarcoglycans, and sarcospan) made of several members or isoforms, and assembled with either dystrophin or its autosomal homologue utrophin (Fig. 1). The DGC has been studied mainly in the context of muscle dystrophies and cardiomyopathies [1–3]. It is critical for integrity of muscle fibers by linking the actin cytoskeleton to the extracellular matrix (ECM) [4–8]. More recently, its roles as a signaling complex and as a scaffold for membrane proteins have gained preeminence. Furthermore, the DGC has been recognized to be molecularly heterogeneous and present in numerous tissues, notably in the central and peripheral nervous system, and in tissues with secretory function or forming barriers between functional compartments, such as the blood-brain barrier (BBB), choroid plexus (CP), or kidney. While the functional role of 'non-muscle' DGC remains to be clarified in most of these organs, there is compelling evidence for its involvement in brain development, synapse formation and plasticity, as well as water and ion homeostasis. The analysis of mice carrying spontaneous or targeted mutations affecting specific DGC components has clarified the interdependence of DGC proteins for assembly of the complex. These studies have also shown that despite functional redundancy, dystrophin isoforms and

* Corresponding author.
[+] Present address: Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK.

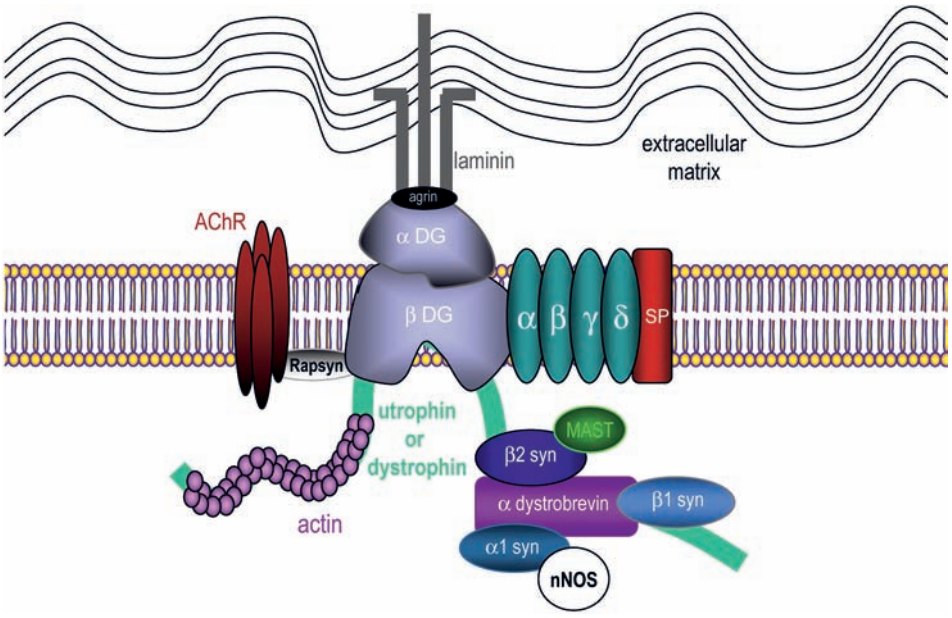

Figure 1. Schematic organization and composition of the DGC at the neuromuscular junction. Dystrophin or utrophin bind to actin filaments via their N terminus. At the C terminus, dystrophin or utrophin are associated with integral and peripheral membrane proteins that can be classified as the dystroglycan complex, the sarcoglycan-sarcospan complex, and the cytoplasmic complex. The cytoplasmic complex includes isoforms of syntrophin (α1-, β1-, β2-syn) and α-dystrobrevin. The sarcoglycan-sarcopsan complex comprises isoforms of sarcoglycan (α, β, γ, δ) and sarcospan (SP). The extracellular component of the dystroglycan complex, α-dystroglycan (α-DG), binds to agrin and laminin in the extracellular matrix and the transmembrane isoform β-dystroglycan (β-DG). In turn, β-dystroglycan binds to dystrophin or utrophin, thus completing the link between the actin-based cytoskeleton and the extracellular matrix. Rapsyn is involved in acetylcholine receptor (AChR) clustering. Signaling proteins such as the microtubule-associated serine/threonine kinase (MAST) or the neuronal nitric oxide synthase (nNOS) are recruited to the DGC via PDZ-binding domains.

utrophin are likely to fulfill distinct roles in non-muscle tissue. Here, we will briefly summarize major features of the DGC in skeletal muscle cells and present an overview of recent developments about the DGC in the brain, BBB, retina, and kidney. The major focus of this review is the role of dystrophin isoforms and utrophin for proper assembly and function of the DGC in these tissues.

The DGC in skeletal muscle

The major components of the DGC have been isolated and characterized best in skeletal muscle cells and will be presented briefly (Fig. 1) before discussing their role and localization in 'non-muscle' tissue. The sarcoglycan complex and sarcospan, which are transmembrane proteins linked to the DGC (Fig. 1), will not be considered in this review.

Dystrophin

The dystrophin gene, located on the X chromosome, spans approximately 2.5 Mb and is composed of 79 exons [9, 10]. Duchenne muscular dystrophy (DMD) is caused by mutations causing a frame-shift and abortion of protein translation. Three independently regulated promoters, in muscle, brain, and specifically Purkinje cells in the cerebellum, control expression of full-length dystrophin [11–17]. In skeletal muscle, dystrophin predominates at the sarcolemma but is also found at the troughs of the postsynaptic membrane along with voltage-gated sodium channels [17, 18]. Several short dystrophin isoforms arise from differential promoter usage. Transcripts from four internal promoters encode proteins of 260, 140, 116, and 71 kDa (Dp260, Dp140, Dp116, and Dp71) [19]. Dp71 is subjected to alternative splicing of exons 71–74 and/or 78, generating at least four Dp71 isoforms [20] with widespread distribution in various non-muscle tissues [21–32]. Full-length dystrophin binds actin near its N terminus and dystroglycan, thereby providing a structural link between the membrane and the cytoskeleton (Fig. 1). Dp71 also carries an actin-binding site [33], suggesting that this short C-terminal isoform fulfills similar functions.

Utrophin

Utrophin was discovered as a cDNA isolated from fetal muscle with high homology to the DMD gene [34]. It is expressed in nearly all tissues, including skeletal muscle, with particularly high levels in lung, kidney, nervous system, and vascular endothelial and smooth muscle cells [25, 31, 32, 35–38], but its function remains largely unknown. Most studies have focused on adult skeletal mus-

cle, where two full-length isoforms of utrophin, differing in their initial few amino acids, have been identified (A- and B-utrophin) [39, 40]. Utrophin is expressed in several structures within skeletal muscle tissue (including blood vessels and nerves) but the dominant utrophin isoform in muscle fibers is A-utrophin. It is confined to the neuromuscular junction (NMJ) and is closely associated with acetylcholine receptors (AChRs) at the crests of the postsynaptic membrane [17, 18, 41–44]. In the present review, no further distinction will be made between the two full-length utrophin isoforms, which are simply referred to as utrophin.

Dystroglycan

Dystroglycan was the first member of the DGC to be cloned [45]. The dystroglycan gene, *DAG1*, comprises two exons and encodes a single polypeptide that is post-translationally cleaved to yield two glycoproteins [46, 47]. Dystroglycan, which anchors the DGC to the sarcolemma and interacts with multiple components of the ECM, is a central component of the complex. Its function critically depends on multiple glycosylation sites which are regulated in a tissue-specific manner [48]. Full chemical deglycosylation of dystroglycan results in loss of ligand-binding activity [5], and abnormal glycosylation is associated with several congenital muscular dystrophies and abnormal central nervous system (CNS) development [2, 49–51]. α-Dystroglycan (α-DG) is located extracellularly where it functions as a laminin/agrin receptor involved in basal membrane formation and synaptogenesis [52–56]. β-Dystroglycan (β-DG) spans the membrane and binds either dystrophin or utrophin at a WW domain near its C terminus. Caveolin 3 binds to the same domain [57], suggesting a potential competitive interaction modulating the membrane anchoring of the DGC [58]. β-DG also binds rapsyn, a protein of the NMJ that is required for clustering of AChRs [59, 60], as well as signaling molecules, such as Grb2, a growth factor receptor-bound adapter protein [61, 62]. The concept that β-DG acts as a scaffolding protein has recently been strengthened by the demonstration that it binds to both MEK and ERK, thereby modulating the ERK-MAP signaling cascade [63].

However, the significance of dystroglycan extends far beyond striated muscle, as it is the most broadly expressed DGC component in both developing and adult tissues [2, 64–66], typically in cell types apposed to a basal lamina [67]. Furthermore, dystroglycan plays an important role in the peripheral nervous system, regulating Schwann cell function and the organization of nodes of Ranvier [68, 69]. Finally, the binding of α-DG to neurexins, neuron-specific cell surface proteins, suggests a novel role for dystroglycan as an intercellular cell adhesion molecule in neurons [70].

Syntrophin

The syntrophin (syn) family is composed of five members, α1-, β1-, β2-, γ1-, and γ2-syn encoded by different genes. α1, β1, β2, and γ2 are expressed in skeletal muscle [71–73]. β2-syn is restricted to the NMJ, whereas α1-, β1-, and γ2-syn are also localized along the sarcolemma [73, 74]. Accordingly, α1- and β1-syn are associated with dystrophin and β2-syn with utrophin [75]. Syntrophins are also expressed in other tissues, such as brain [26, 76–79], retina [80, 81], kidney [32, 82, 83], and liver [84–86]. The γ-syntrophins are most abundant in the brain with γ1-syn being neuron specific [73].

Syntrophins carry a PDZ-binding domain interacting with a variety of signaling molecules and membrane proteins (Fig. 1), including neuronal nitric oxide synthase (nNOS) [87], aquaporin 4 (AQP4) [88], inwardly rectifying K^+ channels [89], muscle voltage-gated sodium channels [77, 90], and stress-activated protein kinase 3 [91]. In addition, β2-syn recruits the serine/threonine kinases MAST and SAST to the DGC [92]. The multiple protein-protein interactions mediated by syntrophins underscore the role of the DGC as a scaffold regulating surface expression of channel proteins and subcellular localization of signaling complexes.

Dystrobrevin

Dystrobrevin is a member of the dystrophin-related protein family with significant homology to the C terminus of dystrophin [93, 94]. Two isoforms, α- and β-dystrobrevin (α- and β-DB), are encoded by different genes [95–97]. The α-DB gene gives rise to at least five splice variants: α-DB1, -2, and -3 are present at the sarcolemma; α-DB1 is restricted to the NMJ whereas α-DB2 has a distribution similar to that of dystrophin [97–99]. Both isoforms bind directly to dystrophin and utrophin through reciprocal coiled-coil regions in each protein [100, 101]. β-DB is absent from striated muscle but is expressed in many non-muscle tissues where it associates with Dp71 and utrophin [26, 29]. A potential signaling molecule containing two MAGE homology domains has recently been identified which selectively binds α-DB and is colocalized with the DGC in brain, muscle, and peripheral nerves [102].

Mutant mice models for studying assembly and function of the DGC

Although no human mutations have been found in genes encoding dystroglycan, syntrophin or dystrobrevin [2, 50], mouse lines carrying targeted gene deletions for these DGC proteins have been generated to study their function. These mutants are presented here in the context of the role and assembly of the DGC in striated muscle and will be discussed in more detail further on.

Dystrophin-null mice

mdx mice [103] lack full-length dystrophin due to a spontaneous point mutation in exon 23 of the DMD gene [104]. These mice exhibit moderate signs of skeletal muscle dystrophy but show little weakness and have a near normal lifespan. This mild phenotype is due in part to compensatory up-regulation of utrophin [105, 106]. However, in the absence of dystrophin, α-DB1 and -2, as well as α1-, β1-, and β2-syn disappear from the sarcolemma but remain at the NMJ [106], where they probably associate with utrophin [75]. The sarcolemmal loss of α1-syn also affects nNOS and AQP4, which are not properly targeted to the membrane in *mdx* mice [107, 108]. Human studies have reported similar findings, showing that α1-syn, α-DB1, and α-DB2 were reduced in muscle from DMD patients [109, 110]. Despite the mild phenotype of *mdx* mice, a typical diagnostic criterion for muscular dystrophies remains: creatine kinase plasma levels are elevated in *mdx* mice [103].

In *mdx* mice, short C-terminal isoforms of dystrophin, such as Dp71, are not affected. Mice lacking all dystrophin isoforms (mdx^{3Cv}) have been generated to overcome this limitation [111, 112]. However, the presence of dystrophin-expressing "revertant" muscle fibers has been reported in both *mdx* and mdx^{3Cv} mice [16], probably due to exon-skipping events occurring during all stages of development. *DMDmdx-βgeo* mice carry a transgene inserted 3′ to exon 63 of the dystrophin gene, affecting translation of all dystrophin isoforms, including Dp71 [113]. These mice develop a dilated esophagus and also cardiac hypertrophy. Both mdx^{3Cv} and *DMDmdx-βgeo* mice display essentially the same muscle pathology as *mdx* mice but have additional defects reflecting the loss of DGC in non-muscle tissue and resulting in a shorter lifespan.

Finally, mutant mice carrying targeted deletions of the DMD gene have been generated [114]. DMD-null males are sterile and exhibit severe degeneration and regeneration of myofibers in striated muscle, as seen in DMD patients [114]. In contrast, mutants with a brain-specific inactivation of full-length dystrophin exhibited no histological abnormality in striated muscle nor in various non-muscle tissues and were indistinguishable from their wild-type littermates [114]. However, a detailed behavioral evaluation of these mice will be necessary to confirm a lack of neurological phenotype.

Utrophin-null mice

Utrophin$^{0/0}$ mice have no morphological defects, breed normally, and have a normal lifespan [115]. Dystrophin expression remains unchanged at the sarcolemma but is up-regulated at the NMJ [116]. In contrast, β-DG and dystrobrevin are normally distributed in utrophin-deficient skeletal muscle. Morphologically, the NMJ of utrophin$^{0/0}$ mice is normal at birth but fewer postsynaptic folds develop thereafter, along with a modest decrease in AChR density [116, 117]. Therefore, utrophin is dispensable for clustering of AChRs at the NMJ, although utrophin is lost from the NMJ in the absence of AChRs [118, 119]. In conclusion, utrophin appears to be dispensable for assembly of a DGC but contributes to proper maturation of the postsynaptic apparatus [60, 117].

Utrophin-dystrophin double-knockout mice

The functional redundancy between utrophin and dystrophin has been confirmed in utrophin$^{0/0}$/*mdx* double-mutant mice, which show major symptoms of DMD, including severe muscle weakness, pronounced growth retardation as well as reduced lifespan [120]. In addition, β-DG is down-regulated, whereas dystrobrevin and β2-syn are undetectable at the NMJ. Nonetheless, laminin-β2, agrin, and rapsyn are unaffected at synapses of utrophin$^{0/0}$/*mdx* mice, indicating that postsynaptic differentiation can occur not only in the absence of both utrophin and dystrophin but also when the DGC is largely disrupted [120]. However, a compensation by dystrobrevin or dystrophin-related protein 2 [121] has not been excluded in these mice.

Syntrophin- and dystrobrevin-null mutations

In α1-syn$^{0/0}$ mice, β1- and β2-syn are up-regulated whereas utrophin is lost from the NMJ, suggesting a mandatory association [75, 122]. In addition, AChRs and ACh esterase are significantly decreased, whereas nNOS is absent from the postsynaptic membrane and the sarcolemma [122]. Mice lacking β2-syn have no apparent muscle phenotype, except for elevated AChR number at the NMJ [123]. That the absence of this protein, which binds to several signaling molecules, does not cause a more severe phenotype is surprising. Even in mice lacking both of these syntrophin isoforms there is no evidence of muscle dystrophy although they run significantly less on voluntary exercise wheels than wild-type mice of either parent strain [123]. In the absence of damage to muscle fibers, this deficit may be due to an unrelated defect, perhaps affecting metabolism or neuronal function. Analysis of the NMJ of α1/β2-syn-null mice has revealed structural defects similar in nature but more severe than those observed in the α1-syn$^{0/0}$ mice. These alterations occurred despite the presence of normal levels of dystrophin, dystrobrevin, and sodium channels [123]. Altogether, these observations point to extensive functional redundancy between α1- and β2-syn.

Analysis of α-DB$^{0/0}$ mice has revealed a dual role for α-DB in the pathogenesis of muscle dystrophy and in AChR stabilization at the NMJ [124, 125]. These mice develop a mild form of dystrophy without disruption of the DGC

at the sarcolemma, indicating that dystrophy might also develop as a result of impaired DGC-dependent signaling. α-DB may be part of a scaffolding or signaling complex required to assemble components of the postsynaptic membrane during synapse formation [126]. Finally, mice lacking β-DB do not suffer from dystrophy since this isoform is not expressed in skeletal muscle. Nevertheless, the DGC is altered at the membrane of cortical renal tubules and hepatic sinusoids [82], underscoring the importance of β-DB in non-muscle tissues.

Mutations affecting dystroglycan

Dystroglycan is essential for embryonic development, as reflected by disruption of the Reichert's membrane surrounding the embryo, resulting in early lethality of null mutant mice [65]. *In vitro*, embryonic stem cells of *DAG1*-null mice form embryoid bodies with a disrupted basement membrane. However, when allowed to differentiate further, these cells can give rise to skeletal muscle, cardiac muscle, and neurons [127]. Furthermore, chimeric mice are rescued from early embryonic lethality and exhibit normal striated muscle differentiation [127]. These mice have severely reduced levels of utrophin and AChRs at the NMJ, confirming the critical role of dystroglycan in the formation of the NMJ [47].

Importantly, dystroglycan function is severely impaired by glycosylation defects. Mutations in at least six genes encoding glycosylation enzymes are associated with congenital muscular dystrophies or myopathies [51, 128–132] commonly termed dystroglycanopathies [50]. The mutations are associated with hypoglycosylation of α-DG and concomitant loss of binding to laminin, agrin, neurexin, or perlecan [133–137]. For instance, the *Large* gene, which encodes a putative bifunctional glycosyltransferase, is mutated in the myodystrophy (*myd*) mouse [133] and in congenital muscular dystrophy type 1D (MDC1D) [138]. *myd* mice exhibit deficits in neuronal migration (lissencephaly), runting, an abnormal gait, cardiomyopathy, and have a shortened lifespan. Surprisingly, dystrophin and other DGC members are still present at the sarcolemma of muscle cells devoid of dystroglycan [139, 140], suggesting alternative mechanisms for membrane anchoring of the DGC [50]. The significance of dystroglycanopathies in the brain will be discussed below.

Altogether, the results summarized in this section show that muscle dystrophies are associated with loss-of-function mutations independently affecting multiple members of the DGC. The phenotype of most animal models is not identical to that of patients with congenital muscle dystrophies, probably due to the complex, tissue-specific roles assumed by the DGC. These results also show that the function and assembly mechanisms of the DGC in skeletal muscle cells cannot be generalized to non-muscle tissues because most functions depend on partner proteins with a cell-specific distribution and regulation.

The DGC in non-muscle tissues

In striated muscle cells, three major functional domains can be distinguished in the DGC: (i) the actin-binding domain of utrophin or dystrophin which links the complex to the cytoskeleton; (ii) the transmembrane protein β-DG and its peripheral isoform α-DG which anchor the DGC to the cell membrane and provide contact with the ECM; (iii) the binding sites to signaling proteins located on β-DG, syntrophin, and dystrobrevin. In non-muscle tissues, the DGC typically contains fewer components associated with a short C-terminal isoform of dystrophin, such as Dp71 or with utrophin, although the failure to detect some DGC members may be due to technical limitations. Nevertheless, the DGC is usually concentrated at membranes facing a basal lamina, suggesting an important signaling function, and its components carry binding sites for membrane channels or transporters. Below, we review recent developments in the molecular composition, localization, and functional role of the DGC in four major organs and tissues: brain, BBB and CP, retina, and kidney, in which the DGC has been characterized extensively in mutant mice.

Brain

Studies of the DGC in brain have addressed mainly its role in mediating brain abnormalities and mental retardation affecting numerous patients with congenital muscle dystrophies, as well as its role in synapse formation and plasticity [141–146]. Members of the DGC are present in specific neurons, astrocytes, and radial glia [19, 23, 26, 30, 35, 37, 64, 145, 147–155], usually associated with either dystrophin isoforms or with utrophin. Thus, full-length dystrophin is neuron specific and is present in the hippocampus, cerebral cortex, and cerebellum, associated with dystroglycan, as well as dystrobrevin and syntrophins [26, 76, 151, 156, 157]. Dp140 is present selectively in the CNS and kidney and is particularly highly expressed prenatally; it is distributed primarily in astrocytic processes, outlining blood vessels and in the meninges [158]. Dp71 is present in dentate gyrus granule cells and in the olfactory bulb [23, 159] and is predominantly found in astrocytes (see below). Utrophin has a distribution in neurons largely complementary to dystrophin, being highly abundant in brainstem [37]. Moreover, utrophin is highly expressed in brain microvessel endothelial cells (see below).

Dystroglycan has a widespread distribution in the brain, including regions lacking dystrophin and utrophin [64, 155]. Besides its distribution in neurons with other DGC

members, dystroglycan is highly abundant in astrocytes, such as the Bergman glia [151, 160] and glial limitans [49, 135]. In neurons, the DGC is localized postsynaptically at inhibitory synapses, colocalizing with $GABA_A$ receptors [153, 157, 158]. However, other studies have shown that dystrophin, β-DB, and syntrophins are enriched in preparations of postsynaptic densities (PSDs) [147, 161, 162], suggesting that both inhibitory and excitatory synapses might contain a DGC. The functional significance of the DGC in PSDs is further underscored by the binding of nNOS to α1-syn [78, 87]. In turn, nNOS binds to PSD-93 and PSD-95, which are involved in N-methyl D-aspartate (NMDA) receptor clustering [87]. Therefore, the DGC might recruit nNOS in excitatory synapses, where it is activated by NMDA-receptor-mediated Ca^{2+} influx. This hypothesis is further supported by the demonstration that nNOS mRNA expression depends on dystrophin in cultured human neurons [163].

To understand whether alterations in the DGC in neurons underlie cognitive impairments in DMD patients, *mdx* mice have been extensively studied for defects of neuronal function. At the morphological level, the absence of full-length dystrophin is accompanied by impaired synaptic clustering of $GABA_A$ receptors [153], suggesting a role for dystrophin in regulating GABAergic transmission in a subset of inhibitory synapses. Thus, this deficit has been associated with a reduction in inhibitory transmission in Purkinje cells [164] and with altered short- and long-term synaptic plasticity in CA1 pyramidal cells [165, 166]. While some studies have observed no impairment in spatial learning or long-term potentiation in the absence of dystrophin [167, 168], a reassessment of *mdx* mice has revealed altered long-term retention, but not acquisition in both spatial and non-spatial learning tasks [166]. mdx^{3Cv} mice show enhanced anxiety-related behaviors and reduced locomotion but are otherwise no more impaired than *mdx* mice in learning and memory tasks [169], which is in line with the predominant expression of full-length dystrophin in hippocampal pyramidal cells.

Pathological studies of brains of DMD patients with cognitive impairments have shown reductions in brain weight, preferential loss of neuronal populations that normally express dystrophin, and small cortical ischemic infarcts [141], suggesting that the absence of dystrophin increases neuronal susceptibility against hypoxia-induced injury. In line with this hypothesis, CA1 pyramidal neurons in a hippocampal slice preparation of *mdx* mice have been found to be more vulnerable to hypoxia [170] and could be protected by pretreatment with diphenylhydantoin, an anticonvulsant that blocks both sodium-dependent action potentials and low-threshold transient calcium channels. This increased neuronal vulnerability might contribute to the development of cognitive deficits in DMD patients [170].

The role of utrophin in brain is not known. Interestingly, unlike in muscle cells, utrophin is not aggregated at postsynaptic sites but is localized along the membrane of neuronal somata and proximal dendrites [37], suggesting that its function is unrelated to synaptic transmission. A potential neuroprotective role of utrophin has been uncovered in a mouse model of temporal lobe epilepsy induced upon unilateral injection of kainic acid into the dorsal hippocampus of adult mice [171], and in which extensive dispersion and hypertrophy of granule cells occur in the dentate gyrus. These changes are accompanied by a prominent overexpression of utrophin in granule cells [159]. $Utrophin^{0/0}$ mice exhibit an increased sensitivity to kainate-induced excitotoxicity, as shown by increased mortality and faster progression of the lesion [172] and a significant reduction in the number of hypertrophic granule cells, suggesting that utrophin contributes to protect these neurons against pathological insults, in particular stimuli leading to cellular hypertrophy [172].

By far the major functional contribution of the DGC in brain is assumed by dystroglycan, as revealed by the profound brain malformations occurring in muscle-eye-brain disease and in Fukuyama congenital muscular dystrophy [173, 174], two congenital muscle dystrophies associated with α-DG loss of function due to mutations in glycosylation enzymes [135]. Similar brain malformations could be reproduced experimentally in *myd* mice [135] and in mutant mice with a brain-specific deletion of *DAG1* under the control of an astrocyte-specific promoter [49], demonstrating that dystroglycan requires glycosylation for proper function and is essential for regulating cell migration and differentiation during development, as well as synaptic plasticity in adult brain. In the brain of *myd* mice, other members of the DGC, including dystrophin, were not targeted appropriately to postsynaptic sites and to glial endfeet [135], underscoring the role of dystroglycan-mediated function for this process, unlike in striated muscle cells. Despite this deficit, dystroglycan-deficient neurons in culture form synapses containing $GABA_A$ receptors and gephyrin clusters opposite GABAergic terminals [158], indicating that the DGC is not required for the development of these synapses.

Altogether, these findings reveal that the DGC expressed in cells of the astrocytic lineage plays an essential role during brain development, whereas the neuronal DGC, which is localized selectively in specific subsets of synapses in adult brain, most likely modulates synaptic function and plasticity, and might be neuroprotective against ischemic damage and other stimuli leading to hypertrophy. This conclusion is in line with reports that full-length dystrophin expression becomes detectable during the third postnatal week in rodents [37], after neuronal migration and synaptogenesis are largely completed. The reason why the DGC is restricted to specific neuronal populations in the brain is open to speculation.

BBB and CP

Endothelial cells of brain microvessels form the BBB, thereby contributing to the protection of the brain against variations in the chemical composition of the blood [175]. Astrocytes contribute to the formation of the BBB during development by inducing tight junctions between endothelial cells [176]. Brain vessels, including capillaries, are a prominent site of expression of DGC proteins, expressed in both endothelial cells and astrocytic endfeet [26, 37, 79, 177–179]. In addition, DGC proteins are also present in the CP [31], suggesting a potential role in water homeostasis and regulation of transport mechanisms across the BBB, as well as cerebrospinal fluid production.

Utrophin is abundantly expressed along with β2-syn in brain endothelial cells [31, 37] but not in astrocytic endfeet (Fig. 2) [31]. In these studies, no other DGC member protein, including Dp71 and dystroglycan, has been detected in endothelial cells of brain capillaries, unlike previous reports describing the presence of dystroglycan in brain blood vessels [96, 155]. The discrepancy between these results might reflect a possible heterogeneity between capillaries and arterioles. In any case, the molecular composition of the DGC in endothelial cells appears to be simpler than in striated muscle or in neurons.

No β2-syn immunoreactivity is detectable in brain blood vessels from utrophin$^{0/0}$ mice, demonstrating a direct association of these proteins in endothelial cells [31], as in striated muscle. However, the loss of utrophin and β2-syn did not affect the localization of the MRP2-type of ABC transporter or the glucose transporter 1 (GLUT1), which are present in the luminal membrane of endothelial cells in the brain [31]. So far, we do not know whether specific signaling proteins or transporters are associated with the DGC in endothelial cells. No alteration in staining for utrophin and β2-syn could be observed in brain blood vessels of *mdx*^{3Cv} mice [31], in agreement with the absence of detectable Dp71 in endothelial cells of wild-type mice (Fig. 2). However, the absence of Dp71 from astrocytic endfeet (see below) during development has been suggested to affect the development of the BBB, leading to an altered expression of the tight junction marker zonula occludens 1 (ZO-1) in old *mdx* mice [180]. These authors therefore speculate that altered cross-talk between glial endfeet and endothelial cells in the absence of dystrophin might contribute to the neurological dysfunctions associated with DMD [181].

Astrocytic endfeet surrounding brain blood vessels exhibit prominent Dp71 expression (Fig. 2) along with β-DG, syntrophin isoforms, and α-DB1 [26, 31, 182–184]. High-resolution immunoelectron microscopy studies have demonstrated that AQP4 and the inwardly rectifying K^+ channel, Kir4.1, are localized selectively in the astrocytic membrane that is in direct contact with the basal lamina facing the blood vessel [179, 185–187]. Both proteins bind to the PDZ domain of α1-syn [185], suggesting that the DGC anchors these proteins at the membrane. The importance of this association has been demonstrated in α-syn$^{0/0}$ mice, in which the membrane localization of AQP4 and Kir4.1 is disrupted, causing a delay in clearance of extracellular K^+ after neuronal activation and an increase in seizure susceptibility [178, 185, 188, 189].

In *mdx*^{3Cv} mice, no DGC proteins can be detected at perivascular endfeet of astrocytes [31], suggesting a complete disruption of the DGC affecting also the localization of AQP4 [190]. However, earlier studies reported that syntrophin, dystrobrevin, and dystroglycan were not altered in these mice [26, 112]. While these discrepancies might reflect incomplete penetrance of the mutation, expression of DGC proteins, as detected by Western blotting, may remain unaltered in mutant mice even when their localization is disrupted.

In CP epithelium, a DGC distinct from those found in brain microvessels has been described [31, 37, 191]. It is formed by utrophin along with β1- and β2-syn and β-DB [31]. Unexpectedly, β-DG was not detected in CP epithelial cells, whereas α-DG was targeted apically [31] despite the presence of a basal lamina between the epithelial cells and the underlying endothelium. Therefore, it remains unclear how the DGC is anchored at the epithelial cell membrane and whether it is linked to the ECM. In CP of utrophin$^{0/0}$ mice, β1- and β2-syn were undetectable whereas β-DB was mislocalized to an intracellular compartment, suggesting that these proteins are differentially dependent on utrophin for proper membrane targeting [31]. These alterations had no apparent consequences for the morphology of epithelial cells, although no compensation by full-length dystrophin or Dp71, which are normally not detectable in the CP, could be observed in utrophin$^{0/0}$ mice [31].

Taken together, these observations suggest the presence of at least three distinct DGCs in the BBB and CP. The analysis of mutant mice shows a clear dependence of DGC proteins for the presence of either Dp71 or utrophin for proper assembly of the complex, and provides no evidence for compensatory up-regulation of another member of the DGC. While the function of the DGC at the BBB and in the CP remains to be uncovered, its role as a scaffold for membrane anchoring of AQP4 and Kir4.1 channels is well established in astrocytic endfeet.

Retina

In analogy to the brain, multiple molecularly distinct DGCs are found in the retina, notably in photoreceptors, neurons, Muller glial cells (MGCs), and blood vessels [192–194]. The predominant dystrophin isoforms are full-length dystrophin, Dp260, Dp140, and Dp71; utrophin is also present, mainly at the same sites as Dp71 [195–200].

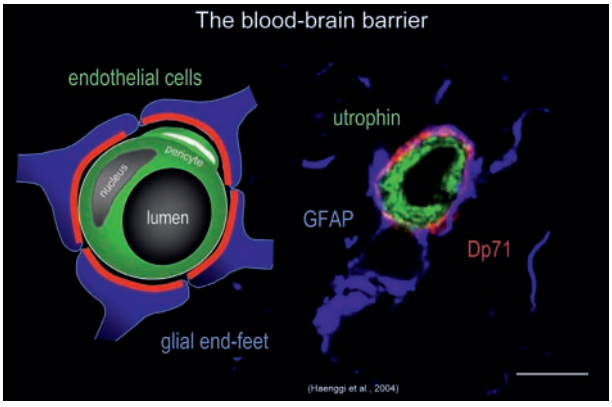

Figure 2. Segregated distribution of utrophin (green) and Dp71 (red) at the BBB and in astrocytic endfeet (GFAP-staining, blue). A schematic representation of a blood vessel surrounded by endfeet is depicted on the left. Utrophin immunoreactivity is localized in endothelial cells, whereas Dp71 overlaps with the GFAP signal in glial endfeet forming a ring around the blood vessel. Scale bar, 5 µm.

In the outer plexiform layer (OPL), where photoreceptors form synapses with horizontal and bipolar cells, the DGC contains dystrophin, dystroglycan, α1-syn, and α-DB [80, 199, 201]. The organization of the DGC differs from that of other neurons, being localized presynaptically in photoreceptor terminals [197, 198, 202–207]. Possible species differences exist, with both a pre- and a postsynaptic DGC being present in the OPL of rabbit and porcine retina [81, 207]. A DGC of similar composition is found also at the IPL (synapses between bipolar/amacrine cells and ganglion cells), although α-DG was not detectable [199]. In contrast, an atypical DGC is found at the outer segment (OS) of photoreceptors, containing β-DG and α1-syn but lacking either dystrophin or utrophin [199].

A major DGC is present in the inner retina where MGC endfeet join to form the inner limiting membrane (ILM), separating the retina from the vitreous body. Across this barrier, K^+ ions are released into the vitreal space through Kir4.1 channels, which are concentrated at the MGC endfeet [208], contributing to K^+ buffering [209]. In addition, AQP4 is localized at the perivascular membrane of MGC endfeet [210] to control retinal water transport [211]. Several members of the DGC have been detected in MGCs (β-DG, α1-, β1-syn, α-DB) and their endfeet (Dp71, utrophin, dystroglycan) [28, 199–201, 208, 212]. The complex associates with Kir4.1 and AQP4, similar to the DGC found in perivascular astrocytic endfeet in brain, and most likely fulfills a similar functional role [213].

The segregation of various DGCs to different retinal layers has allowed detailed analyses of the role of dystrophin isoforms for their assembly and subcellular localization. For example, in retina of *mdx*^{3Cv} mice, β-DG protein levels are reduced in the ILM and OPL [199], whereas α1-syn and α-DB are not affected [199]. Furthermore, clustering of Kir4.1 is disrupted in MGC endfeet of *mdx*^{3Cv} [208]; unexpectedly, it is not affected in α1-syn$^{0/0}$ mice [212], pointing to a differential mechanism compared with brain blood vessels. Partial disruption of the DGC has also been reported in the retina of Dp71-null mice, which exhibit reduced levels of β-DG at the ILM, whereas α1-syn is

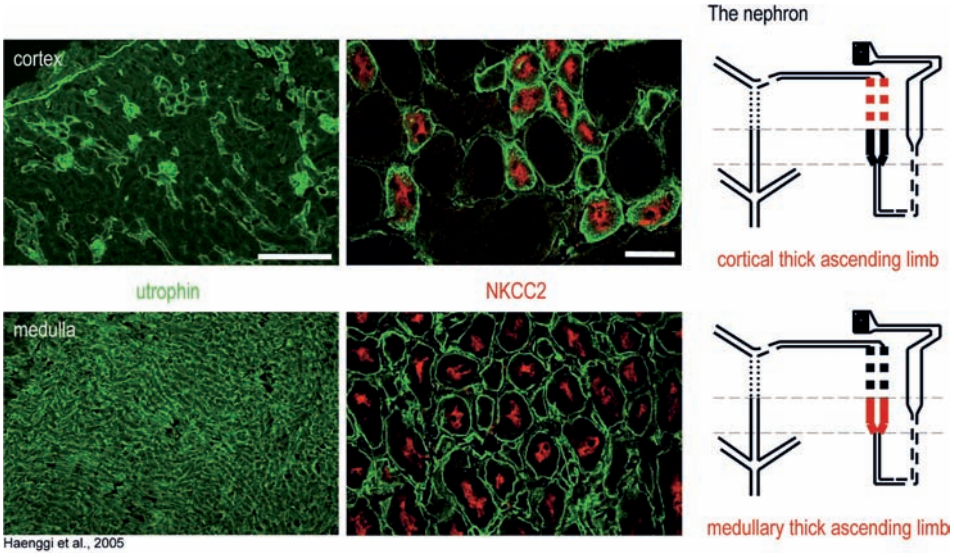

Figure 3. Differential expression and cellular distribution of utrophin in mouse kidney. A schematic drawing of the nephron is depicted on the right panel. The cortical and medullary thick ascending limbs are colored in red. Low-resolution immunofluorescence images (left panel) depict utrophin (green) distribution in the cortex and medulla. In the cortex, utrophin staining is heterogeneous, labeling glomeruli and few cortical segments. Using a renal segment-specific marker, the $Na^+/K^+/Cl^-$ cotransporter 2 (NKCC2) (red, right panel), which is polarized along the apical membrane of cortical and medullary thick ascending limbs, we could identify a utrophin-positive segments. In the medulla, utrophin exhibits a homogenous distribution and double staining with NKCC2 revealed medullary thick ascending limbs as utrophin-positive segment (lower middle panel). More renal markers have been investigated [32]. Scale bars, 200 µm (utrophin), 30 µm (NKCC2).

not affected [200]. Unlike in *mdx*^{3Cv} mice, β-DG expression is normal at the OPL, possibly due to association with Dp260 [200]. Therefore, Dp71 is important for the assembly of the DGC selectively in MGC endfeet. This conclusion is supported by the fact that β-DG is disrupted at the OPL of mice lacking full-length dystrophin and Dp260 [214, 215].

The retina also provides a functional read-out applicable for both mutant mice and DMD patients. Indeed, electroretinogram (ERG) anomalies are among the best-characterized non-muscular manifestations of DMD. Analysis of the dark-adapted ERG has revealed a reduction in the amplitude of the b-wave response in 80% of DMD patients [216–219]. A prolonged implicit time of the b-wave has been observed in ERG of mice lacking full-length dystrophin and Dp260 [215], whereas Dp71-null mice showed no significant change [200]. By comparing ERG alterations in patients with distinct mutations, Pillers et al. [220] suggested that in addition to Dp260, other C-terminal isoforms contribute to the generation of the b-wave. This hypothesis was confirmed by the demonstration that *mdx*^{3Cv} have b-waves with reduced amplitude and increased implicit time [221].

As expected from studies in the brain, *myd* mice exhibit major morphological alterations in the retina, affecting MGCs as well as neurons. A similar phenotype was seen, in addition, in a novel mutant mouse line, *Large*^{vls} mice [134, 222]. These mice carry a mutation in a new allele of *Large*, named veils (vls), and share phenotypic characteristics with the *myd* mutation [222]. These findings confirm that defective dystroglycan glycosylation contributes to retinal abnormalities.

Kidney

Epithelial cells in the nephron express numerous DGC proteins, forming several distinct DGCs. As the nephron is organized in distinct segments to sequentially reabsorb ions and solutes from the glomerular ultrafiltrate, it represents an attractive organ to study the localization and specific distribution of DGC proteins [29, 32, 66, 223–225]. Dystroglycan is expressed early by epithelial cells in the developing kidney, whereas in adult tissue only low levels are detectable [66, 67], suggesting that dystroglycan is more important for morphogenesis of renal epithelial cells than during the adult stage. Similarly to dystroglycan, Dp140 is only expressed during kidney development [226]. Low levels of Dp71 are detectable in adult kidney [32, 82, 224, 226–230], although a specific splice variant has been reported to be abundant, in particular in the cortex [29]. In contrast, utrophin is prominent in all segments of the nephron except proximal tubules (Fig. 3) [32]. On the subcellular level, utrophin is specifically localized along the basal, but not lateral, membrane of tubular epithelial cells, demonstrating that it is restricted to sites of contact with the basal lamina (Fig. 3). In contrast, the DGC is polarized along the basolateral membrane of cultured kidney epithelial cells [231], suggesting altered targeting *in vitro* in the absence of the basal lamina. Using specific markers to identify distinct segments of the nephron, utrophin has been shown to be associated with different members of the DGC in a segment-specific manner (Fig. 3). In particular, α1- and β1-syn have a restricted distribution, whereas β2-syn and β-DB are ubiquitous [29, 32]. These findings indicate that Dp71 isoforms and utrophin are the major partners of the DGC in the nephron and that the functional specialization of the tubule is reflected in the segment-specific distribution of certain DGC proteins.

Possible alterations in DGC assembly and targeting have been investigated in *mdx*^{3Cv} mice to test the role of Dp71. β2-syn staining was altered in cortical renal tubules, Bowman's capsule and glomeruli, whereas the localization of β-DB, α-DB-1, utrophin, α1-syn and β1-syn was not affected [29]. These findings suggest differential dependence of β2-syn and other DGC proteins on Dp71 for complex formation. In a complementary study using utrophin$^{0/0}$ mice, we have demonstrated that β2-syn localization is not impaired in cortical segments in the absence of utrophin, whereas it is lost in all segments expressing high utrophin levels in wild-type mice [32]. Again, other DGC proteins were either not affected in mutant mice (β1- and α1-syn) or were upregulated (Dp71, β-DG, and dystrobrevin) (Fig. 4), indicating that compensatory mechanisms are activated to preserve most of the DGC in either *mdx*^{3Cv} or utrophin$^{0/0}$ mice [32].

To directly demonstrate this compensatory up-regulation, utrophin-deficient mice were cross-bred with *mdx*^{3Cv} mice to generate utrophin$^{0/0}$/*mdx*^{3Cv} double mutants. These mice have a reduced lifespan [120], and only few reach the adult stage. Nevertheless, analysis of the nephron has revealed a complete disruption of the DGC, highlighting the functional redundancy between utrophin and dystrophin in cells coexpressing both proteins [32].

The complex, segment-specific molecular organization of the DGC in the nephron suggests multiple functional roles related to ion transport mechanisms. In analogy to skeletal muscle cells, where the DGC provides membrane stability during muscle contractions [4], renal epithelial cells might also have a DGC to resist the high osmotic pressure of the hypertonic interstitial fluid surrounding medullary tubules [232]. The high abundance of utrophin in these segments of the nephron, unlike in the renal cortex, supports this idea. Although Dp71 is upregulated in utrophin$^{0/0}$ mice, the compensation is only partial because β2-syn is lost from the DGC. The reduced life expectancy of double-mutant mice where no compensation is possible in the kidney might be due to renal dysfunction. However, this hypothesis remains to be tested.

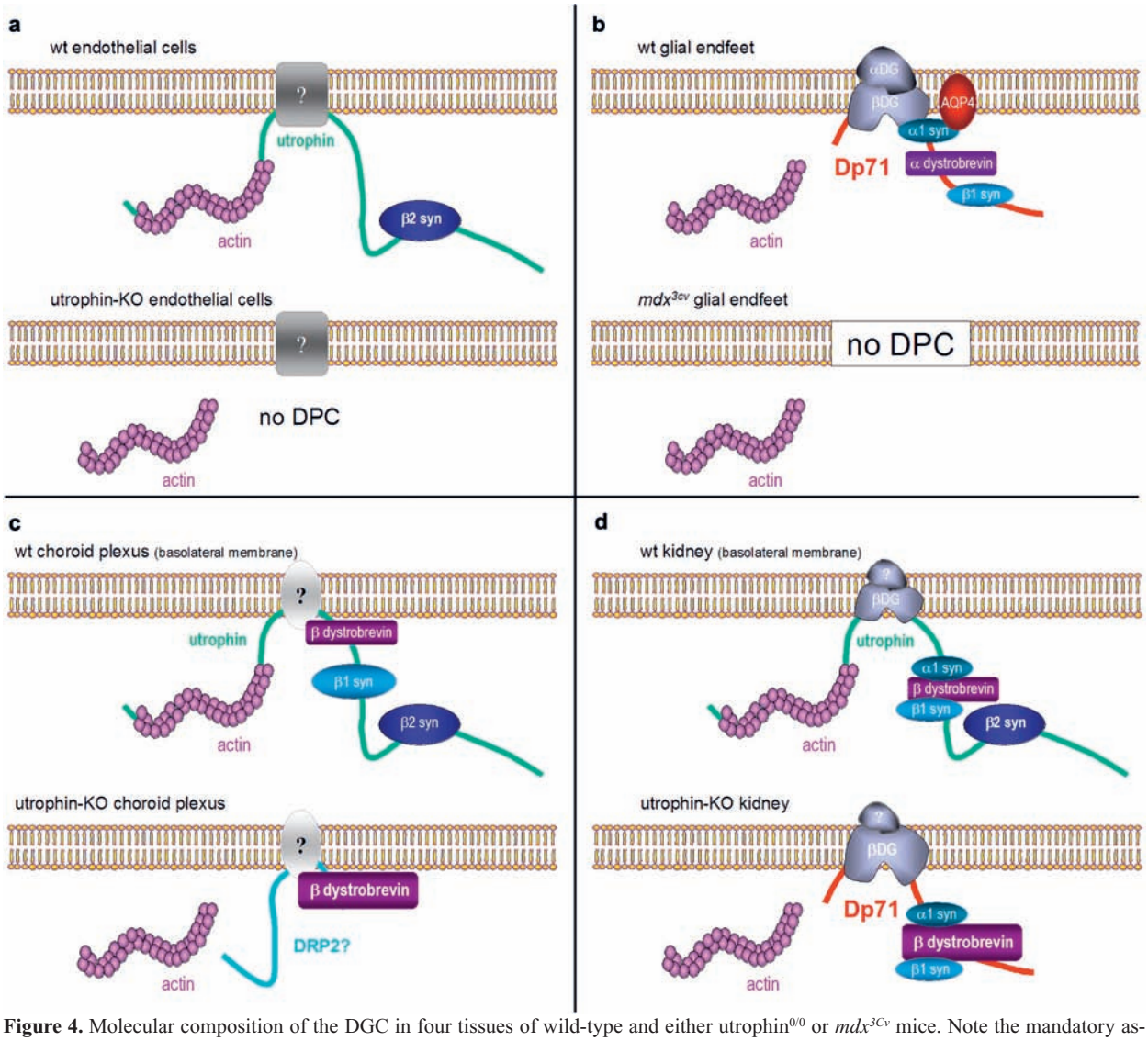

Figure 4. Molecular composition of the DGC in four tissues of wild-type and either utrophin$^{0/0}$ or *mdx*^{3Cv} mice. Note the mandatory association of β2-syn with utrophin in kidney, CP, and endothelial cells. In utrophin$^{0/0}$ kidney, the DPC is partially rescued by compensatory upregulation of Dp71, but it is unclear whether it binds the actin cytoskeleton. In blood vessels (endothelial and glial endfeet), no compensation occurs and the DPC is disrupted, along with AQP4. An intermediate situation occurs in the CP, where β-DB is partially retained, possibly due to upregulation of dystrophin-related protein 2 (DRP2).

Finally, for proper function of renal epithelial cells, ion channels, exchangers, and transporters must be targeted to either the apical or basolateral membrane [233]. The DGC may be involved in anchoring renal transporters and channels to the basal membrane. So far, however, no protein has been identified for which the DGC serves as a scaffolding protein, similarly to AQP4 and Kir4.1 in astrocytes.

Conclusions

The characterization of the DGC in non-muscle tissues has revealed an unexpected heterogeneity in molecular composition, in particular with respect to the presence of α- or β-DG. The mechanism of membrane anchoring and/or communication with the ECM is therefore not established for some prominent DGCs, such as those seen in microvascular endothelial cells and the CP. However, negative results are not necessarily conclusive, and the failure to detect dystroglycan in some tissues might be due to technical reasons. Furthermore, some biochemical methods are of limited use in heterogeneous tissues with a cell-specific expression of DGC proteins. It is important to note that in neurons and astrocytes, as well as kidney tubular epithelial cells, the localization of the DGC precisely matches the presence of a basal lamina, suggesting that communication with the ECM via α-DG is essential for specifying the subcellular localization of the DGC. This feature might, for example, explain the

remarkably specific targeting of the DGC in astrocytic endfeet. In the CP, the DGC is present basolaterally in epithelial cells, arguing against the presence of dystroglycan in this tissue.

The analysis of mutant mice has revealed that in all cell types coexpressing a dystrophin isoform with utrophin, compensatory up-regulation takes place in the absence of the homologue protein (Fig. 4), obscuring the interpretation of the analysis of single mutant mice. In contrast, these compensatory mechanisms do not take place in tissues expressing only dystrophin (glial endfeet) or only utrophin (CP epithelial cells, vascular endothelial cells). The analysis of double-mutant mice lacking dystrophin and utrophin is hampered by the severe phenotype, limited breeding capacity, and reduced life expectancy of these animals.

A major convergent finding emerging from the analysis of the DGC in non-muscle tissue is that syntrophins require the presence of either dystrophin or utrophin for assembly of the DGC and membrane localization. Owing to the presence of several 'simple' DGCs containing a reduced number of proteins, a mandatory association of β2-syn with utrophin, as well as α-DB, α1-syn, and β1-syn with dystrophin, has been demonstrated in three distinct tissues (Fig. 4). The role of β-DB is less clear since it does not disappear from the CP of utrophin$^{0/0}$ mice and associates with Dp71 in the absence of utrophin in the kidney. Therefore, although dystroglycan is a key member of the DGC, interacting with signaling proteins, dystrophin and utrophin appear to be essential for the formation of the complex, with very few exceptions so far [234].

Several membrane-associated proteins have been identified, notably AQP4 and Kir4.1, which depend on the DGC for proper targeting and localization. However, no generalization is possible since major transporters, such as members of the ABC transporter or the glucose transporter families, which colocalize with the DGC in several tissues, are not affected in mutant mice. It is therefore difficult to predict functional deficits that might arise from an altered expression of DGC proteins. However, the existence of functional redundancy between dystrophin isoforms, dystrobrevin, and utrophin might represent a strong stimulus for exploiting further compensatory mechanisms to alleviate the symptoms of muscle dystrophy.

Acknowledgements. Our work is supported by the Swiss National Science Foundation. We are grateful to our colleagues M. C. Schaub, R. Züllig, B. Bornhauser, and I. Knüsel for their contribution at various phases of the project and for advice and support. We thank C. Sidler, F. Parpan and T. Grampp for excellent technical assistance.

1 Blake, D. J., Weir A., Newey, S. E. and Davies, K. E. (2002) Function and genetics of dystrophin and dystrophin-related proteins in muscle. Physiol. Rev. 82, 291–329.
2 Durbeej M. and Campbell, K. P. (2002) Muscular dystrophies involving the dystrophin-glycoprotein complex: an overview of current mouse models. Curr. Opin. Genet. Dev. 12, 349–361.
3 Cohen N. and Muntoni F. (2004) Multiple pathogenetic mechanisms in X linked dilated cardiomyopathy. Heart 90, 835–841.
4 Petrof, B. J., Shrager, J. B., Stedman, H. H., Kelly, A. M. and Sweeney, H. L. (1993) Dystrophin protects the sarcolemma from stresses developed during muscle contraction. Proc. Natl. Acad. Sci. USA 90, 3710–3714.
5 Ervasti, J. M. and Campbell, K. P. (1993) A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. J. Cell Biol. 122, 809–823.
6 Mora M., Morandi L., Piccinelli A., Gussoni E., Gebbia M., Blasevich F., Dworzak F. and Cornelio F. (1993) Dystrophin abnormalities in Duchenne and Becker dystrophy carriers: correlation with cytoskeletal proteins and myosins. J. Neurol. 240, 455–461.
7 Campbell, K. P. (1995) Three muscular dystrophies: loss of cytoskeleton-extracellular matrix linkage. Cell 80, 675–679.
8 Lapidos, K. A., Kakkar R. and McNally, E. M. (2004) The dystrophin glycoprotein complex: signaling strength and integrity for the sarcolemma. Circ. Res. 94, 1023–1031.
9 Koenig M., Hoffman, E. P., Bertelson, C. J., Monaco, A. P., Feener C. and Kunkel, L. M. (1987) Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell 50, 509–517.
10 Love, D. R., Bloomfield, J. F., Kenwrick, S. J., Yates, J. R. and Davies, K. E. (1990) Physical mapping distal to the DMD locus. Genomics 8, 106–112.
11 Nudel U., Zuk D., Einat P., Zeelon E., Levy Z., Neuman S. and Yaffe D. (1989) Duchenne muscular dystrophy gene product is not identical in muscle and brain. Nature 337, 76–78.
12 Chelly J., Hamard G., Koulakoff A., Kaplan, J. C., Kahn A. and Berwald-Netter Y. (1990) Dystrophin gene transcribed from different promoters in neuronal and glial cells. Nature 344, 64–65.
13 Klamut, H. J., Gangopadhyay, S. B., Worton, R. G. and Ray, P. N. (1990) Molecular and functional analysis of the muscle-specific promoter region of the Duchenne muscular dystrophy gene. Mol. Cell Biol. 10, 193–205.
14 Boyce, F. M., Beggs, A. H., Feener C. and Kunkel, L. M. (1991) Dystrophin is transcribed in brain from a distant upstream promoter. Proc. Natl. Acad. Sci. USA 88, 1276–1280.
15 Gorecki D., Geng Y., Thomas K., Hunt, S. P., Barnard, E. A. and Barnard, P. J. (1991) Expression of the dystrophin gene in mouse and rat brain. Neuroreport 2, 773–776.
16 Makover A., Zuk D., Breakstone J., Yaffe D. and Nudel U. (1991) Brain-type and muscle-type promoters of the dystrophin gene differ greatly in structure. Neuromuscul. Disord. 1, 39–45.
17 Berthier C. and Blaineau S. (1997) Supramolecular organization of the subsarcolemmal cytoskeleton of adult skeletal muscle fibers: a review. Biol. Cell 89, 413–434.
18 Sealock R., Butler, M. H., Kramarcy, N. R., Gao, K. X., Murnane, A. A., Douville K. and Froehner, S. C. (1991) Localization of dystrophin relative to acetylcholine receptor domains in electric tissue and adult and cultured skeletal muscle. J. Cell Biol. 113, 1133–1144.
19 Gorecki, D. C., Monaco, A. P., Derry, J. M., Walker, A. P., Barnard, E. A. and Barnard, P. J. (1992) Expression of four alternative dystrophin transcripts in brain regions regulated by different promoters. Hum. Mol. Genet. 1, 505–510.
20 Gonzalez E., Montanez C., Ray, P. N., Howard, P. L., Garcia-Sierra F., Mornet D. and Cisneros B. (2000) Alternative splicing regulates the nuclear or cytoplasmic localization of dystrophin Dp71. FEBS Lett. 482, 209–214.
21 Jung D., Filliol D., Metz-Boutigue, M. H. and Rendon A. (1993) Characterization and subcellular localization of the

dystrophin-protein 71 (Dp71) from brain. Neuromuscul. Disord. 3, 515–518.
22 Tamura T., Yoshioka K., Jinno Y., Niikawa N. and Miike T. (1993) Dystrophin isoforms expressed in the mouse retina. J. Neurol. Sci. 115, 214–218.
23 Gorecki, D. C. and Barnard, E. A. (1995) Specific expression of G-dystrophin (Dp71) in the brain. Neuroreport 6, 893–896.
24 Ueda H., Tsukahara S., Kobayashi T. and Ohno S. (1995) Immunocytochemical study of dystrophin-related protein in the rat retina. Ophthal. Res. 27, 219–226.
25 Imamura M. and Ozawa E. (1998) Differential expression of dystrophin isoforms and utrophin during dibutyryl-cAMP-induced morphological differentiation of rat brain astrocytes. Proc. Natl. Acad. Sci. USA 95, 6139–6144.
26 Blake, D. J., Hawkes R., Benson, M. A. and Beesley, P. W. (1999) Different dystrophin-like complexes are expressed in neurons and glia. J. Cell Biol. 147, 645–658.
27 Austin, R. C., Morris, G. E., Howard, P. L., Klamut, H. J. and Ray, P. N. (2000) Expression and synthesis of alternatively spliced variants of Dp71 in adult human brain. Neuromuscul. Disord. 10, 187–193.
28 Claudepierre T., Mornet D., Pannicke T., Forster V., Dalloz C., Bolanos F., Sahel J., Reichenbach A. and Rendon A. (2000) Expression of Dp71 in Müller glial cells: a comparison with utrophin- and dystrophin-associated proteins. Invest. Ophthalmol. Vis. Sci. 41, 294–304.
29 Loh, N. Y., Newey, S. E., Davies, K. E. and Blake, D. J. (2000) Assembly of multiple dystrobrevin-containing complexes in the kidney. J. Cell Sci. 113, 2715–2724.
30 Aleman V., Osorio B., Chavez O., Rendon A., Mornet D. and Martinez D. (2001) Subcellular localization of Dp71 dystrophin isoforms in cultured hippocampal neurons and forebrain astrocytes. Histochem. Cell. Biol. 115, 243–254.
31 Haenggi T., Soontornmalai A., Schaub, M. C. and Fritschy, J. M. (2004) The role of utrophin and Dp71 for assembly of different dystrophin-associated protein complexes (DPCs) in the choroid plexus and microvasculature of the brain. Neuroscience 129, 403–413.
32 Haenggi T., Schaub, M. C. and Fritschy, J. M. (2005) Molecular heterogeneity of the dystrophin-associated protein complex in the mouse kidney nephron: differential alterations in the absence of utrophin and dystrophin. Cell Tissue Res. 319, 299–313.
33 Howard, P. L., Klamut, H. J. and Ray, P. N. (1998) Identification of a novel actin binding site within the Dp71 dystrophin isoform. FEBS Lett. 441, 337–341.
34 Love, D. R., Hill, D. F., Dickson G., Spurr, N. K., Byth, B. C., Marsden, R. F., Walsh, F. S., Edwards, Y. H. and Davies, K. E. (1989) An autosomal transcript in skeletal muscle with homology to dystrophin. Nature 339, 55–58.
35 Blake, D. J., Schofield, J. N., Zuellig, R. A., Gorecki, D. C., Phelps, S. R., Barnard, E. A., Edwards, Y. H. and Davies, K. E. (1995) G-utrophin, the autosomal homologue of dystrophin Dp116, is expressed in sensory ganglia and brain. Proc. Natl. Acad. Sci. USA 92, 3697–3701.
36 Lumeng, C. N., Phelps, S. F., Rafael, J. A., Cox, G. A., Hutchinson, T. L., Begy, C. R., Adkins E., Wiltshire R. and Chamberlain, J. S. (1999) Characterization of dystrophin and utrophin diversity in the mouse. Hum. Mol. Genet. 8, 593–599.
37 Knuesel I., Bornhauser, B. C., Zuellig, R. A., Heller F., Schaub, M. C. and Fritschy, J. M. (2000) Differential expression of utrophin and dystrophin in CNS neurons: an in situ hybridization and immunohistochemical study. J. Comp. Neurol. 422, 594–611.
38 Sogos V., Curto M., Reali C. and Gremo F. (2002) Developmentally regulated expression and localization of dystrophin and utrophin in the human fetal brain. Mech. Ageing Dev. 123, 455–462.
39 Burton, E. A., Tinsley, J. M., Holzfeind, P. J., Rodrigues, N. R. and Davies, K. E. (1999) A second promoter provides an alternative target for therapeutic up-regulation of utrophin in Duchenne muscular dystrophy. Proc. Natl. Acad. Sci. USA 96, 14025–14030.
40 Weir, A. P., Burton, E. A., Harrod G. and Davies, K. E. (2002) A- and B-utrophin have different expression patterns and are differentially up-regulated in mdx muscle. J. Biol. Chem. 277, 45285–45290.
41 Byers, T. J., Kunkel, L. M. and Watkins, S. C. (1991) The subcellular distribution of dystrophin in mouse skeletal, cardiac, and smooth muscle. J. Cell Biol. 115, 411–421.
42 Khurana, T. S., Watkins, S. C., Chafey P., Chelly J., Tome, F. M., Fardeau M., Kaplan, J. C. and Kunkel, L. M. (1991) Immunolocalization and developmental expression of dystrophin related protein in skeletal muscle. Neuromuscul. Disord. 1, 185–194.
43 Ohlendieck K., Ervasti, J. M., Matsumura K., Kahl, S. D., Leveille, C. J. and Campbell, K. P. (1991) Dystrophin-related protein is localized to neuromuscular junctions of adult skeletal muscle. Neuron 7, 499–508.
44 Bewick, G. S., Nicholson, L. V., Young C., O'Donnell E. and Slater, C. R. (1992) Different distributions of dystrophin and related proteins at nerve-muscle junctions. Neuroreport 3, 857–860.
45 Ibraghimov-Beskrovnaya O., Ervasti, J. M., Leveille, C. J., Slaughter, C. A., Sernett, S. W. and Campbell, K. P. (1992) Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. Nature 355, 696–702.
46 Chamberlain J. (1999) The dynamics of dystroglycan. Nat. Genet. 23, 256–258.
47 Winder, S. J. (2001) The complexities of dystroglycan. Trends Biochem. Sci. 26, 118–124.
48 Durbeej M., Henry, M. D. and Campbell, K. P. (1998) Dystroglycan in development and disease. Curr. Opin. Cell Biol. 10, 594–601.
49 Moore, S. A., Saito F., Chen J., Michele, D. E., Henry, M. D., Messing A., Cohn, R. D., Ross-Barta, S. E., Westra S., Williamson, R. A., Hoshi T. and Campbell, K. P. (2002) Deletion of brain dystroglycan recapitulates aspects of congenital muscular dystrophy. Nature 418, 422–425.
50 Michele, D. E. and Campbell, K. P. (2003) Dystrophin-glycoprotein complex: post-translational processing and dystroglycan function. J. Biol. Chem. 278, 15457–15460.
51 Haliloglu G. and Topaloglu H. (2004) Glycosylation defects in muscular dystrophies. Curr Opin Neurol. 17, 521–527.
52 Jacobson C., Montanaro F., Lindenbaum M., Carbonetto S. and Ferns M. (1998) α-Dystroglycan functions in acetylcholine receptor aggregation but is not a coreceptor for agrin-MuSK signaling. J. Neurosci. 18, 6340–6348.
53 Montanaro F., Gee, S. H., Jacobson C., Lindenbaum, M. H., Froehner, S. C. and Carbonetto S. (1998) Laminin and α-dystroglycan mediate acetylcholine receptor aggregation via a MuSK-independent pathway. J. Neurosci. 18, 1250–1260.
54 Montanaro F., Lindenbaum M. and Carbonetto S. (1999) α-Dystroglycan is a laminin receptor involved in extracellular matrix assembly on myotubes and muscle cell viability. J. Cell Biol. 145, 1325–1340.
55 Henry, M. D., Satz, J. S., Brakebusch C., Costell M., Gustafsson E., Fassler R. and Campbell, K. P. (2001) Distinct roles for dystroglycan, beta1 integrin and perlecan in cell surface laminin organization. J. Cell Sci. 114, 1137–1144.
56 Jacobson C., Cote, P. D., Rossi, S. G., Rotundo, R. L. and Carbonetto S. (2001) The dystroglycan complex is necessary for stabilization of acetylcholine receptor clusters at neuromuscular junctions and formation of the synaptic basement membrane. J. Cell Biol. 152, 435–450.
57 Song, K. S., Scherer, P. E., Tang Z., Okamoto T., Li S., Chafel M., Chu C., Kohtz, D. S. and Lisanti, M. P. (1996) Expression

of caveolin-3 in skeletal, cardiac, and smooth muscle cells: caveolin-3 is a component of the sarcolemma and co-fractionates with dystrophin and dystrophin-associated glycoproteins. J. Biol. Chem. 271, 15160–15165.
58 Ilsley, J. L., Sudol M. and Winder, S. J. (2002) The WW domain: linking cell signalling to the membrane cytoskeleton. Cell Signal. 14, 183–189.
59 Cartaud A., Coutant S., Petrucci, T. C. and Cartaud J. (1998) Evidence for in situ and *in vitro* association between β-dystroglycan and the subsynaptic 43K rapsyn protein: consequence for acetylcholine receptor clustering at the synapse. J. Biol. Chem. 273, 11321–11326.
60 Banks, G. B., Fuhrer C., Adams, M. E. and Froehner, S. C. (2003) The postsynaptic submembrane machinery at the neuromuscular junction: requirement for rapsyn and the utrophin/dystrophin-associated complex. J. Neurocytol. 32, 709–726.
61 Cavaldesi M., Macchia G., Barca S., Defilippi P., Tarone G. and Petrucci, T. C. (1999) Association of the dystroglycan complex isolated from bovine brain synaptosomes with proteins involved in signal transduction. J. Neurochem. 72, 1648–1655.
62 Yang B., Jung D., Motto D., Meyer J., Koretzky G. and Campbell, K. P. (1995) SH3 domain-mediated interaction of dystroglycan and Grb2. J. Biol. Chem. 270, 11711–11714.
63 Spence, H. J., Dhillon, A. S., James M. and Winder, S. J. (2004) Dystroglycan, a scaffold for the ERK-MAP kinase cascade. EMBO Rep. 5, 484–489.
64 Gorecki, D. C., Derry, J. M. and Barnard, E. A. (1994) Dystroglycan: brain localisation and chromosome mapping in the mouse. Hum. Mol. Genet. 3, 1589–1597.
65 Williamson, R. A., Henry, M. D., Daniels, K. J., Hrstka, R. F., Lee, J. C., Sunada Y., Ibraghimov-Beskrovnaya O. and Campbell, K. P. (1997) Dystroglycan is essential for early embryonic development: disruption of Reichert's membrane in Dag1-null mice. Hum. Mol. Genet. 6, 831–841.
66 Durbeej M., Henry, M. D., Ferletta M., Campbell, K. P. and Ekblom P. (1998) Distribution of dystroglycan in normal adult mouse tissues. J. Histochem. Cytochem. 46, 449–457.
67 Durbeej M., Larsson E., Ibraghimov-Beskrovnaya O., Roberds, S. L., Campbell, K. P. and Ekblom P. (1995) Non-muscle α-dystroglycan is involved in epithelial development. J. Cell Biol. 130, 79–91.
68 Saito F., Moore, S. A., Barresi R., Henry, M. D., Messing A., Ross-Barta, S. E., Cohn, R. D., Williamson, R. A., Sluka, K. A., Sherman, D. L., Brophy, P. J., Schmelzer, J. D., Low, P. A., Wrabetz L., Feltri, M. L. and Campbell, K. P. (2003) Unique role of dystroglycan in peripheral nerve myelination, nodal structure, and sodium channel stabilization. Neuron 38, 747–758.
69 Occhi S., Zambroni D., Del Carro U., Amadio S., Sirkowski, E. E., Scherer, S. S., Campbell, K. P., Moore, S. A., Chen, Z. L., Strickland S., Di Muzio A., Uncini A., Wrabetz L. and Feltri, M. L. (2005) Both laminin and Schwann cell dystroglycan are necessary for proper clustering of sodium channels at nodes of ranvier. J. Neurosci. 25, 9418–9427.
70 Sugita S., Saito F., Tang J., Satz J., Campbell K. and Sudhof, T. C. (2001) A stoichiometric complex of neurexins and dystroglycan in brain. J. Cell Biol. 154, 435–445.
71 Adams, M. E., Butler, M. H., Dwyer, T. M., Peters, M. F., Murnane, A. A. and Froehner, S. C. (1993) Two forms of mouse syntrophin, a 58-kd dystrophin-associated protein, differ in primary structure and tissue distribution. Neuron 11, 531–540.
72 Ahn, A. H., Yoshida M., Anderson, M. S., Feener, C. A., Selig S., Hagiwara Y., Ozawa E. and Kunkel, L. M. (1994) Cloning of human basic A1, a distinct 59-kDa dystrophin-associated protein encoded on chromosome 8q23–24. Proc. Natl. Acad. Sci. USA 91, 4446–4450.
73 Piluso G., Mirabella M., Ricci E., Belsito A., Abbondanza C., Servidei S., Puca, A. A., Tonali P., Puca, G. A. and Nigro V. (2000) γ1- and γ2-syntrophins, two novel dystrophin-binding proteins localized in neuronal cells. J. Biol. Chem. 275, 15851–15860.
74 Peters, M. F., Kramarcy, N. R., Sealock R. and Froehner, S. C. (1994) β2-Syntrophin: localization at the neuromuscular junction in skeletal muscle. Neuroreport 5, 1577–1580.
75 Peters, M. F., Adams, M. E. and Froehner, S. C. (1997) Differential association of syntrophin pairs with the dystrophin complex. J. Cell Biol. 138, 81–93.
76 Gorecki, D. C., Abdulrazzak H., Lukasiuk K. and Barnard, E. A. (1997) Differential expression of syntrophins and analysis of alternatively spliced dystrophin transcripts in the mouse brain. Eur. J. Neurosci. 9, 965–976.
77 Gee, S. H., Madhavan R., Levinson, S. R., Caldwell, J. H., Sealock R. and Froehner, S. C. (1998) Interaction of muscle and brain sodium channels with multiple members of the syntrophin family of dystrophin-associated proteins. J. Neurosci. 18, 128–137.
78 Hashida-Okumura A., Okumura N., Iwamatsu A., Buijs, R. M., Romijn, H. J. and Nagai K. (1999) Interaction of neuronal nitric-oxide synthase with alpha1-syntrophin in rat brain. J. Biol. Chem. 274, 11736–11741.
79 Inoue M., Wakayama Y., Liu, J. W., Murahashi M., Shibuya S. and Oniki H. (2002) Ultrastructural localization of aquaporin 4 and alpha1-syntrophin in the vascular feet of brain astrocytes. Tohoku J. Exp. Med. 197, 87–93.
80 Claudepierre T., Dalloz C., Mornet D., Matsumura K., Sahel J. and Rendon A. (2000) Characterization of the intermolecular associations of the dystrophin-associated glycoprotein complex in retinal Müller glial cells. J. Cell Sci. 113, 3409–3417.
81 Bordais A., Bolanos-Jimenez F., Fort P., Varela C., Sahel, J. A., Picaud S. and Rendon A. (2005) Molecular cloning and protein expression of Duchenne muscular dystrophy gene products in porcine retina. Neuromuscul. Disord. 15, 476–487.
82 Loh, N. Y., Nebenius-Oosthuizen D., Blake, D. J., Smith, A. J. and Davies, K. E. (2001) Role of β-dystrobrevin in nonmuscle dystrophin-associated protein complex-like complexes in kidney and liver. Mol. Cell. Biol. 21, 7442–7448.
83 Munehira Y., Ohnishi T., Kawamoto S., Furuya A., Shitara K., Imamura M., Yokota T., Takeda S., Amachi T., Matsuo M., Kioka N. and Ueda K. (2004) α1-syntrophin modulates turnover of ABCA1. J. Biol. Chem. 279, 15091–15095.
84 Loh, N. Y., Ambrose, H. J., Guay-Woodford, L. M., DasGupta S., Nawrotzki, R. A., Blake, D. J. and Davies, K. E. (1998) Genomic organization and refined mapping of the mouse β-dystrobrevin gene. Mamm. Genome 9, 857–862.
85 Buechler C., Boettcher A., Bared, S. M., Probst, M. C. and Schmitz G. (2002) The carboxyterminus of the ATP-binding cassette transporter A1 interacts with a β2-syntrophin/utrophin complex. Biochem. Biophys. Res. Commun. 293, 759–765.
86 Schmitz G. and Langmann T. (2005) Transcriptional regulatory networks in lipid metabolism control ABCA1 expression. Biochim. Biophys. Acta 1735, 1–19.
87 Brenman, J. E., Chao, D. S., Gee, S. H., McGee, A. W., Craven, S. E., Santillano, D. R., Wu Z., Huang F., Xia H., Peters, M. F., Froehner, S. C. and Bredt, D. S. (1996) Interaction of nitric oxide synthase with the postsynaptic density protein PSD-95 and α1-syntrophin mediated by PDZ domains. Cell 84, 757–767.
88 Adams, M. E., Mueller, H. A. and Froehner, S. C. (2001) *In vivo* requirement of the α-syntrophin PDZ domain for the sarcolemmal localization of nNOS and aquaporin-4. J. Cell Biol. 155, 113–122.
89 Leonoudakis D., Conti, L. R., Anderson S., Radeke, C. M., McGuire, L. M., Adams, M. E., Froehner, S. C., Yates, J. R. and Vandenberg, C. A. (2004) Protein trafficking and anchoring complexes revealed by proteomic analysis of inward rectifier potassium channel (Kir2.x)-associated proteins. J. Biol. Chem. 279, 22331–22346.

90 Schultz J., Hoffmuller U., Krause G., Ashurst J., Macias, M. J., Schmieder P., Schneider-Mergener J. and Oschkinat H. (1998) Specific interactions between the syntrophin PDZ domain and voltage-gated sodium channels. Nat. Struct. Biol. 5, 19–24.

91 Hasegawa M., Cuenda A., Spillantini, M. G., Thomas, G. M., Buee-Scherrer V., Cohen P. and Goedert M. (1999) Stress-activated protein kinase-3 interacts with the PDZ domain of α1-syntrophin. A mechanism for specific substrate recognition. J. Biol. Chem. 274, 12626–12631.

92 Lumeng C., Phelps S., Crawford, G. E., Walden, P. D., Barald K. and Chamberlain, J. S. (1999) Interactions between β2-syntrophin and a family of microtubule-associated serine/threonine kinases. Nat. Neurosci. 2, 611–617.

93 Wagner, K. R., Cohen, J. B. and Huganir, R. L. (1993) The 87-kDa postsynaptic membrane protein from Torpedo is a protein-tyrosine kinase substrate homologous to dystrophin. Neuron 10, 511–522.

94 Blake, D. J., Nawrotzki R., Peters, M. F., Froehner, S. C. and Davies, K. E. (1996) Isoform diversity of dystrobrevin, the murine 87-kDa postsynaptic protein. J. Biol. Chem. 271, 7802–7810.

95 Peters, M. F., O'Brien, K. F., Sadoulet-Puccio, H. M., Kunkel, L. M., Adams, M. E. and Froehner, S. C. (1997) β-Dystrobrevin, a new member of the dystrophin family: identification, cloning, and protein associations. J. Biol. Chem. 272, 31561–31569.

96 Blake, D. J., Nawrotzki R., Loh, N. Y., Gorecki, D. C. and Davies, K. E. (1998) β-Dystrobrevin, a member of the dystrophin-related protein family. Proc. Natl. Acad. Sci. USA 95, 241–246.

97 Nawrotzki R., Loh, N. Y., Ruegg, M. A., Davies, K. E. and Blake, D. J. (1998) Characterisation of α-dystrobrevin in muscle. J. Cell Sci. 111, 2595–2605.

98 Peters, M. F., Sadoulet-Puccio, H. M., Grady, M. R., Kramarcy, N. R., Kunkel, L. M., Sanes, J. R., Sealock R. and Froehner, S. C. (1998) Differential membrane localization and intermolecular associations of α-dystrobrevin isoforms in skeletal muscle. J. Cell Biol. 142, 1269–1278.

99 Newey, S. E., Gramolini, A. O., Wu J., Holzfeind P., Jasmin, B. J., Davies, K. E. and Blake, D. J. (2001) A novel mechanism for modulating synaptic gene expression: differential localization of α-dystrobrevin transcripts in skeletal muscle. Mol. Cell. Neurosci. 17, 127–140.

100 Blake, D. J., Tinsley, J. M., Davies, K. E., Knight, A. E., Winder, S. J. and Kendrick-Jones J. (1995) Coiled-coil regions in the carboxy-terminal domains of dystrophin and related proteins: potentials for protein-protein interactions. Trends Biochem. Sci. 20, 133–135.

101 Sadoulet-Puccio, H. M., Rajala M. and Kunkel, L. M. (1997) Dystrobrevin and dystrophin: an interaction through coiled-coil motifs. Proc. Natl. Acad. Sci. USA 94, 12413–12418.

102 Albrecht, D. E. and Froehner, S. C. (2004) DAMAGE, a novel alpha-dystrobrevin-associated MAGE protein in dystrophin complexes. J. Biol. Chem. 279, 7014–7023.

103 Bulfield G., Siller, W. G., Wight, P. A. and Moore, K. J. (1984) X chromosome-linked muscular dystrophy (mdx) in the mouse. Proc. Natl. Acad. Sci. USA 81, 1189–1192.

104 Ryder-Cook, A. S., Sicinski P., Thomas K., Davies, K. E., Worton, R. G., Barnard, E. A., Darlison, M. G. and Barnard, P. J. (1988) Localization of the mdx mutation within the mouse dystrophin gene. EMBO J. 7, 3017–3021.

105 Takemitsu M., Ishiura S., Koga R., Kamakura K., Arahata K., Nonaka I. and Sugita H. (1991) Dystrophin-related protein in the fetal and denervated skeletal muscles of normal and mdx mice. Biochem. Biophys. Res. Commun. 14, 1179–1186.

106 Matsumura K., Ervasti, J. M., Ohlendieck K., Kahl, S. D. and Campbell, K. P. (1992) Association of dystrophin-related protein with dystrophin-associated proteins in mdx mouse muscle. Nature 360, 588–591.

107 Thomas, G. D., Sander M., Lau, K. S., Huang, P. L., Stull, J. T. and Victor, R. G. (1998) Impaired metabolic modulation of α-adrenergic vasoconstriction in dystrophin-deficient skeletal muscle. Proc. Natl. Acad. Sci. USA 95, 15090–15095.

108 Frigeri A., Nicchia, G. P., Nico B., Quondamatteo F., Herken R., Roncali L. and Svelto M. (2001) Aquaporin-4 deficiency in skeletal muscle and brain of dystrophic mdx mice. FASEB J. 15, 90–98.

109 Compton, A. G., Cooper, S. T., Hill, P. M., Yang N., Froehner, S. C. and North, K. N. (2005) The syntrophin-dystrobrevin subcomplex in human neuromuscular disorders. J. Neuropathol. Exp. Neurol. 64, 350–361.

110 Metzinger L., Blake, D. J., Squier, M. V., Anderson, L. V., Deconinck, A. E., Nawrotzki R., Hilton-Jones D. and Davies, K. E. (1997) Dystrobrevin deficiency at the sarcolemma of patients with muscular dystrophy. Hum. Mol. Genet. 6, 1185–1191.

111 Cox, G. A., Phelps, S. F., Chapman, V. M. and Chamberlain, J. S. (1993) New mdx mutation disrupts expression of muscle and nonmuscle isoforms of dystrophin. Nat. Genet. 4, 87–93.

112 Culligan K., Glover L., Dowling P. and Ohlendieck K. (2001) Brain dystrophin-glycoprotein complex: persistent expression of β-dystroglycan, impaired oligomerization of Dp71 and up-regulation of utrophins in animal models of muscular dystrophy. BMC Cell. Biol. 2, 2.

113 Wertz K. and Fuchtbauer, E. M. (1998) Dmd(mdx-βgeo): a new allele for the mouse dystrophin gene. Dev. Dyn. 212, 229–241.

114 Kudoh H., Ikeda H., Kakitani M., Ueda A., Hayasaka M., Tomizuka K. and Hanaoka K. (2005) A new model mouse for Duchenne muscular dystrophy produced by 2.4 Mb deletion of dystrophin gene using Cre-loxP recombination system. Biochem. Biophys. Res. Commun. 328, 507–516.

115 Deconinck, A. E., Rafael, J. A., Skinner, J. A., Brown, S. C., Potter, A. C., Metzinger L., Watt, D. J., Dickson, J. G., Tinsley, J. M. and Davies, K. E. (1997) Utrophin-dystrophin-deficient mice as a model for Duchenne muscular dystrophy. Cell 90, 717–727.

116 Deconinck, A. E., Potter, A. C., Tinsley, J. M., Wood, S. J., Vater R., Young C., Metzinger L., Vincent A., Slater, C. R. and Davies, K. E. (1997) Postsynaptic abnormalities at the neuromuscular junctions of utrophin-deficient mice. J. Cell Biol. 136, 883–894.

117 Grady, R. M., Merlie, J. P. and Sanes, J. R. (1997) Subtle neuromuscular defects in utrophin-deficient mice. J. Cell Biol. 136, 871–882.

118 Slater, C. R., Young C., Wood, S. J., Bewick, G. S., Anderson, L. V., Baxter P., Fawcett, P. R., Roberts M., Jacobson L., Kuks J., Vincent A. and Newsom-Davis J. (1997) Utrophin abundance is reduced at neuromuscular junctions of patients with both inherited and acquired acetylcholine receptor deficiencies. Brain 120, 1513–1531.

119 Sieb, J. P., Kraner S., Rauch M. and Steinlein, O. K. (2000) Immature end-plates and utrophin deficiency in congenital myasthenic syndrome caused by ε-AChR subunit truncating mutations. Hum. Genet. 107, 160–164.

120 Grady, R. M., Teng H., Nichol, M. C., Cunningham, J. C., Wilkinson, R. S. and Sanes, J. R. (1997) Skeletal and cardiac myopathies in mice lacking utrophin and dystrophin: a model for Duchenne muscular dystrophy. Cell 90, 729–738.

121 Roberts, R. G., Freeman, T. C., Kendall E., Vetrie, D. L., Dixon, A. K., Shaw-Smith C., Bone Q. and Bobrow M. (1996) Characterization of DRP2, a novel human dystrophin homologue. Nat. Genet. 13, 223–226.

122 Adams, M. E., Kramarcy N., Krall, S. P., Rossi, S. G., Rotundo, R. L., Sealock R. and Froehner, S. C. (2000) Absence of α-syntrophin leads to structurally aberrant neuromuscular synapses deficient in utrophin. J. Cell Biol. 150, 1385–1398.

123 Adams, M. E., Kramarcy N., Fukuda T., Engel, A. G., Sealock R. and Froeher, S. C. (2004) Structural abnormalities at neu-

romuscular synapses lacking multiple syntrophin isoforms. J. Neurosci. 24, 10302–10309.
124 Grady, R. M., Zhou H., Cunningham, J. M., Henry, M. D., Campbell, K. P. and Sanes, J. R. (2000) Maturation and maintenance of the neuromuscular synapse: genetic evidence for roles of the dystrophin-glycoprotein complex. Neuron 25, 279–293.
125 Grady, R. M., Grange, R. W., Lau, K. S., Maimone, M. M., Nichol, M. C., Stull, J. T. and Sanes, J. R. (1999) Role for α-dystrobrevin in the pathogenesis of dystrophin-dependent muscular dystrophies. Nat. Cell Biol. 1, 215–220.
126 Blake, D. J. (2002) Dystrobrevin dynamics in muscle-cell signalling: a possible target for therapeutic intervention in Duchenne muscular dystrophy? Neuromuscul. Disord. 12 Suppl 1, S110–S117.
127 Cote, P. D., Moukhles H., Lindenbaum M. and Carbonetto S. (1999) Chimaeric mice deficient in dystroglycans develop muscular dystrophy and have disrupted myoneural synapses. Nat. Genet. 23, 338–342.
128 Kano H., Kobayashi K., Herrmann R., Tachikawa M., Manya H., Nishino I., Nonaka I., Straub V., Talim B., Voit T., Topaloglu H., Endo T., Yoshikawa H. and Toda T. (2002) Deficiency of α-dystroglycan in muscle-eye-brain disease. Biochem. Biophys. Res. Commun. 291, 1283–1286.
129 Grewal, P. K. and Hewitt, J. E. (2003) Glycosylation defects: a new mechanism for muscular dystrophy? Hum. Mol. Genet. 12 Spec. No. 2, R259–R264.
130 Hewitt, J. E. and Grewal, P. K. (2003) Glycosylation defects in inherited muscle disease. Cell. Mol. Life Sci. 60, 251–258.
131 Martin, P. T. (2003) Glycobiology of the neuromuscular junction. J. Neurocytol. 32, 915–929.
132 Toda T., Kobayashi K., Takeda S., Sasaki J., Kurahashi H., Kano H., Tachikawa M., Wang F., Nagai Y., Taniguchi K., Taniguchi M., Sunada Y., Terashima T., Endo T. and Matsumura K. (2003) Fukuyama-type congenital muscular dystrophy (FCMD) and alpha-dystroglycanopathy. Congenit. Anom. (Kyoto) 43, 97–104.
133 Grewal, P. K., Holzfeind, P. J., Bittner, R. E. and Hewitt, J. E. (2001) Mutant glycosyltransferase and altered glycosylation of α-dystroglycan in the myodystrophy mouse. Nat. Genet. 28, 151–154.
134 Holzfeind, P. J., Grewal, P. K., Reitsamer, H. A., Kechvar J., Lassmann H., Hoeger H., Hewitt, J. E. and Bittner, R. E. (2002) Skeletal, cardiac and tongue muscle pathology, defective retinal transmission, and neuronal migration defects in the Large(myd) mouse defines a natural model for glycosylation-deficient muscle-eye-brain disorders. Hum. Mol. Genet. 11, 2673–2687.
135 Michele, D. E., Barresi R., Kanagawa M., Saito F., Cohn, R. D., Satz, J. S., Dollar J., Nishino I., Kelley, R. I., Somer H., Straub V., Mathews, K. D., Moore, S. A. and Campbell, K. P. (2002) Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. Nature 418, 417–422.
136 Kanagawa M., Saito F., Kunz S., Yoshida-Moriguchi T., Barresi R., Kobayashi, Y. M., Muschler J., Dumanski, J. P., Michele, D. E., Oldstone, M. B. and Campbell, K. P. (2004) Molecular recognition by LARGE is essential for expression of functional dystroglycan. Cell 117, 953–964.
137 Kanagawa M., Michele, D. E., Satz, J. S., Barresi R., Kusano H., Sasaki T., Timpl R., Henry, M. D. and Campbell, K. P. (2005) Disruption of perlecan binding and matrix assembly by post-translational or genetic disruption of dystroglycan function. FEBS Lett. 579, 4792–4796.
138 Longman C., Brockington M., Torelli S., Jimenez-Mallebrera C., Kennedy C., Khalil N., Feng L., Saran, R. K., Voit T., Merlini L., Sewry, C. A., Brown, S. C. and Muntoni F. (2003) Mutations in the human LARGE gene cause MDC1D, a novel form of congenital muscular dystrophy with severe mental retardation and abnormal glycosylation of alpha-dystroglycan. Hum. Mol. Genet. 12, 2853–2861.
139 Cohn, R. D., Henry, M. D., Michele, D. E., Barresi R., Saito F., Moore, S. A., Flanagan, J. D., Skwarchuk, M. W., Robbins, M. E., Mendell, J. R., Williamson, R. A. and Campbell, K. P. (2002) Disruption of DAG1 in differentiated skeletal muscle reveals a role for dystroglycan in muscle regeneration. Cell 110, 639–648.
140 Cote, P. D., Moukhles H. and Carbonetto S. (2002) Dystroglycan is not required for localization of dystrophin, syntrophin, and neuronal nitric-oxide synthase at the sarcolemma but regulates integrin alpha 7B expression and caveolin-3 distribution. J. Biol. Chem. 277, 4672–4679.
141 Rosman, N. P. and Kakulas, B. A. (1966) Mental deficiency associated with muscular dystrophy: a neuropathological study. Brain 89, 769–788.
142 Chamberlain, J. S., Pearlman, J. A., Muzny, D. M., Gibbs, R. A., Ranier, J. E., Caskey, C. T. and Reeves, A. A. (1988) Expression of the murine Duchenne muscular dystrophy gene in muscle and brain. Science 239, 1416–1418.
143 Felisari G., Martinelli Boneschi F., Bardoni A., Sironi M., Comi, G. P., Robotti M., Turconi, A. C., Lai M., Corrao G. and Bresolin N. (2000) Loss of Dp140 dystrophin isoform and intellectual impairment in Duchenne dystrophy. Neurology 55, 559–564.
144 Mehler, M. F. (2000) Brain dystrophin, neurogenetics and mental retardation. Brain Res. Brain Res. Rev 32, 277–307.
145 Moizard, M. P., Billard C., Toutain A., Berret F., Marmin N. and Moraine C. (1998) Are Dp71 and Dp140 brain dystrophin isoforms related to cognitive impairment in Duchenne muscular dystrophy? Am. J. Med. Genet. 80, 32–41.
146 Moizard, M. P., Toutain A., Fournier D., Berret F., Raynaud M., Billard C., Andres C. and Moraine C. (2000) Severe cognitive impairment in DMD: obvious clinical indication for Dp71 isoform point mutation screening. Eur. J. Hum. Genet. 8, 552–556.
147 Lidov, H. G., Byers, T. J., Watkins, S. C. and Kunkel, L. M. (1990) Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. Nature 348, 725–728.
148 Gee, S. H., Blacher, R. W., Douville, P. J., Provost, P. R., Yurchenco, P. D. and Carbonetto S. (1993) Laminin-binding protein 120 from brain is closely related to the dystrophin-associated glycoprotein, dystroglycan, and binds with high affinity to the major heparin binding domain of laminin. J. Biol. Chem. 268, 14972–14980.
149 Lidov, H. G. (1996) Dystrophin in the nervous system. Brain Pathol. 6, 63–77.
150 Mummery R., Sessay A., Lai, F. A. and Beesley, P. W. (1996) β-Dystroglycan: subcellular localisation in rat brain and detection of a novel immunologically related, postsynaptic density-enriched protein. J. Neurochem. 66, 2455–2459.
151 Tian M., Jacobson C., Gee, S. H., Campbell, K. P., Carbonetto S. and Jucker M. (1996) Dystroglycan in the cerebellum is a laminin alpha 2-chain binding protein at the glial-vascular interface and is expressed in Purkinje cells. Eur. J. Neurosci. 8, 2739–2747.
152 Finn, D. M., Culligan, K. G. and Ohlendieck K. (1998) Decreased expression of brain β-dystroglycan in Duchenne muscular dystrophy but not in the mdx animal model. Biochem. Biophys. Res. Commun. 249, 231–235.
153 Knuesel I., Mastrocola M., Zuellig, R. A., Bornhauser B., Schaub, M. C. and Fritschy, J. M. (1999) Short communication: altered synaptic clustering of $GABA_A$ receptors in mice lacking dystrophin (mdx mice). Eur. J. Neurosci. 11, 4457–4462.
154 Moukhles H. and Carbonetto S. (2001) Dystroglycan contributes to the formation of multiple dystrophin-like complexes in brain. J. Neurochem. 78, 824–834.

155 Zaccaria, M. L., Di Tommaso F., Brancaccio A., Paggi P. and Petrucci, T. C. (2001) Dystroglycan distribution in adult mouse brain: a light and electron microscopy study. Neuroscience 104, 311–324.

156 Brunig I., Suter A., Knuesel I., Luscher B. and Fritschy, J. M. (2002) GABAergic terminals are required for postsynaptic clustering of dystrophin but not of GABA(*a*) receptors and gephyrin. J. Neurosci. 22, 4805–4813.

157 Levi S., Grady, R. M., Henry, M. D., Campbell, K. P., Sanes, J. R. and Craig, A. M. (2002) Dystroglycan is selectively associated with inhibitory GABAergic synapses but is dispensable for their differentiation. J. Neurosci. 22, 4274–4285.

158 Lidov, H. G., Selig S. and Kunkel, L. M. (1995) Dp140: a novel 140 kDa CNS transcript from the dystrophin locus. Hum. Mol. Genet. 4, 329–335.

159 Knuesel I., Zuellig, R. A., Schaub, M. C. and Fritschy, J. M. (2001) Alterations in dystrophin and utrophin expression parallel the reorganization of GABAergic synapses in a mouse model of temporal lobe epilepsy. Eur. J. Neurosci. 13, 1113–1124.

160 Henion, T. R., Qu Q. and Smith, F. I. (2003) Expression of dystroglycan, fukutin and POMGnT1 during mouse cerebellar development. Mol. Brain Res. 112, 177–181.

161 Lidov, H. G., Byers, T. J. and Kunkel, L. M. (1993) The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. Neuroscience 54, 167–187.

162 Kim, T. W., Wu K., Xu, J. L. and Black, I. B. (1992) Detection of dystrophin in the postsynaptic density of rat brain and deficiency in a mouse model of Duchenne muscular dystrophy. Proc. Natl. Acad. Sci. USA 89, 11642–11644.

163 Sogos V., Reali C., Fanni V., Curto M. and Gremo F. (2003) Dystrophin antisense oligonucleotides decrease expression of nNOS in human neurons. Brain Res. Mol. Brain Res. 118, 52–59.

164 Anderson, J. L., Head, S. I. and Morley, J. W. (2003) Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. Brain Res. 982, 280–283.

165 Vaillend C. and Billard, J. M. (2002) Facilitated CA1 hippocampal synaptic plasticity in dystrophin-deficient mice: role for GABAA receptors? Hippocampus 12, 713–717.

166 Vaillend C., Billard, J. M. and Laroche S. (2004) Impaired long-term spatial and recognition memory and enhanced CA1 hippocampal LTP in the dystrophin-deficient Dmd(mdx) mouse. Neurobiol. Dis. 17, 10–20.

167 Muntoni F., Mateddu A. and Serra G. (1991) Passive avoidance behaviour deficit in the mdx mouse. Neuromuscul. Disord. 1, 121–123.

168 Sesay, A. K., Errington, M. L., Levita L. and Bliss, T. V. (1996) Spatial learning and hippocampal long-term potentiation are not impaired in mdx mice. Neurosci. Lett. 211, 207–210.

169 Vaillend C. and Ungerer A. (1999) Behavioral characterization of *mdx*^{3cv} mice deficient in C-terminal dystrophins. Neuromuscul. Disord. 9, 296–304.

170 Mehler, M. F., Haas, K. Z., Kessler, J. A. and Stanton, P. K. (1992) Enhanced sensitivity of hippocampal pyramidal neurons from mdx mice to hypoxia-induced loss of synaptic transmission. Proc. Natl. Acad. Sci. USA 89, 2461–2465.

171 Bouilleret V., Ridoux V., Depaulis A., Marescaux C., Nehlig A. and Le Gal La Salle G. (1999) Recurrent seizures and hippocampal sclerosis following intrahippocampal kainate injection in adult mice: electroencephalography, histopathology and synaptic reorganization similar to mesial temporal lobe epilepsy. Neuroscience 89, 717–729.

172 Knuesel I., Riban V., Zuellig, R. A., Schaub, M. C., Grady, R. M., Sanes, J. R. and Fritschy, J. M. (2002) Increased vulnerability to kainate-induced seizures in utrophin-knockout mice. Eur. J. Neurosci. 15, 1474–1484.

173 Dubowitz V. (2000) Congenital muscular dystrophy: an expanding clinical syndrome. Ann. Neurol. 47, 143–144.

174 Toda T., Kobayashi K., Kondo-Iida E., Sasaki J. and Nakamura Y. (2000) The Fukuyama congenital muscular dystrophy story. Neuromuscul. Disord. 10, 153–159.

175 Rubin, L. L. and Staddon, J. M. (1999) The cell biology of the blood-brain barrier. Annu. Rev. Neurosci. 22, 11–28.

176 Neuwelt, E. A. (2004) Mechanisms of disease: the blood-brain barrier. Neurosurgery 54, 131–142.

177 Guadagno E. and Moukhles H. (2004) Laminin-induced aggregation of the inwardly rectifying potassium channel, Kir4.1, and the water-permeable channel, AQP4, via a dystroglycan-containing complex in astrocytes. Glia 47, 138–149.

178 Amiry-Moghaddam M., Xue R., Haug, F. M., Neely, J. D., Bhardwaj A., Agre P., Adams, M. E., Froehner, S. C., Mori S. and Ottersen, O. P. (2004) α-Syntrophin deletion removes the perivascular but not endothelial pool of aquaporin-4 at the blood-brain barrier and delays the development of brain edema in an experimental model of acute hyponatremia. FASEB J. 18, 542–544.

179 Connors, N. C., Adams, M. E., Froehner, S. C. and Kofuji P. (2004) The potassium channel Kir4.1 associates with the dystrophin-glycoprotein complex via α-syntrophin in glia. J. Biol. Chem. 279, 28387–28392.

180 Nico B., Frigeri A., Nicchia, G. P., Corsi P., Ribatti D., Quondamatteo F., Herken R., Girolamo F., Marzullo A., Svelto M. and Roncali L. (2003) Severe alterations of endothelial and glial cells in the blood-brain barrier of dystrophic mdx mice. Glia 42, 235–251.

181 Nico B., Paola Nicchia G., Frigeri A., Corsi P., Mangieri D., Ribatti D., Svelto M. and Roncali L. (2004) Altered blood-brain barrier development in dystrophic MDX mice. Neuroscience 125, 921–935.

182 Ueda H., Baba T., Terada N., Kato Y., Fujii Y., Takayama I., Mei X. and Ohno S. (2000) Immunolocalization of dystrobrevin in the astrocytic endfeet and endothelial cells in the rat cerebellum. Neurosci. Lett. 283, 121–124.

183 Warth A., Kroger S. and Wolburg H. (2004) Redistribution of aquaporin-4 in human glioblastoma correlates with loss of agrin immunoreactivity from brain capillary basal laminae. Acta. Neuropathol. (Berl) 109, 418 – 426.

184 Galaz-Vega R., Hernandez-Kelly, L. C., Mendez, J. A., Cisneros B. and Ortega A. (2005) Glutamate regulates dystrophin-71 levels in glia cells. Neurochem. Res. 30, 237–243.

185 Neely, J. D., Amiry-Moghaddam M., Ottersen, O. P., Froehner, S. C., Agre P. and Adams, M. E. (2001) Syntrophin-dependent expression and localization of Aquaporin-4 water channel protein. Proc. Natl. Acad. Sci. USA 98, 14108–14113.

186 Nielsen S., Nagelhus, E. A., Amiry-Moghaddam M., Bourque C., Agre P. and Ottersen, O. P. (1997) Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J. Neurosci. 17, 171–180.

187 Higashi K., Fujita A., Inanobe A., Tanemoto M., Doi K., Kubo T. and Kurachi Y. (2001) An inwardly rectifying K^+ channel, Kir4.1, expressed in astrocytes surrounds synapses and blood vessels in brain. Am. J. Physiol. Cell Physiol. 281, C922–C931.

188 Amiry-Moghaddam M., Otsuka T., Hurn, P. D., Traystman, R. J., Haug, F. M., Froehner, S. C., Adams, M. E., Neely, J. D., Agre P., Ottersen, O. P. and Bhardwaj A. (2003) An α-syntrophin-dependent pool of AQP4 in astroglial end-feet confers bidirectional water flow between blood and brain. Proc. Natl. Acad. Sci. USA 100, 2106–2111.

189 Amiry-Moghaddam M., Frydenlund, D. S. and Ottersen, O. P. (2004) Anchoring of aquaporin-4 in brain: molecular mechanisms and implications for the physiology and pathophysiology of water transport. Neuroscience 129, 999–1010.

190 Greenberg, D. S., Schatz Y., Levy Z., Pizzo P., Yaffe D. and Nudel U. (1996) Reduced levels of dystrophin associated proteins in the brains of mice deficient for Dp71. Hum. Mol. Genet. 5, 1299–1303.

191 Khurana, T. S., Watkins, S. C. and Kunkel, L. M. (1992) The subcellular distribution of chromosome 6-encoded dystrophin-related protein in the brain. J. Cell Biol. 119, 357–366.
192 Schmitz F. and Drenckhahn D. (1997) Dystrophin in the retina. Prog. Neurobiol. 53, 547–560.
193 Ueda H., Baba T. and Ohno S. (2000) Current knowledge of dystrophin and dystrophin-associated proteins in the retina. Histol. Histopathol. 15, 753–760.
194 Blank M., Blake, D. J. and Kroger S. (2002) Molecular diversity of the dystrophin-like protein complex in the developing and adult avian retina. Neuroscience 111, 259–273.
195 Montanaro F., Carbonetto S., Campbell, K. P. and Lindenbaum M. (1995) Dystroglycan expression in the wild-type and mdx mouse neural retina: synaptic colocalization with dystrophin, dystrophin-related protein but not laminin. J. Neurosci. Res. 42, 528–538.
196 Howard, P. L., Dally, G. Y., Wong, M. H., Ho A., Weleber, R. G., Pillers, D. A. and Ray, P. N. (1998) Localization of dystrophin isoform Dp71 to the inner limiting membrane of the retina suggests a unique functional contribution of Dp71 in the retina. Hum. Mol. Genet. 7, 1385–1391.
197 Ueda H., Gohdo T. and Ohno S. (1998) β-Dystroglycan localization in the photoreceptor and Muller cells in the rat retina revealed by immunoelectron microscopy. J. Histochem. Cytochem. 46, 185–191.
198 Blank M., Koulen P., Blake, D. J. and Kroger S. (1999) Dystrophin and β-dystroglycan in photoreceptor terminals from normal and mdx^{3Cv} mouse retinae. Eur. J. Neurosci. 11, 2121–2133.
199 Dalloz C., Claudepierre T., Rodius F., Mornet D., Sahel J. and Rendon A. (2001) Differential distribution of the members of the dystrophin glycoprotein complex in mouse retina: effect of the *mdx^{3Cv}* mutation. Mol. Cell. Neurosci. 17, 908–920.
200 Dalloz C., Sarig R., Fort P., Yaffe D., Bordais A., Pannicke T., Grosche J., Mornet D., Reichenbach A., Sahel J., Nudel U. and Rendon A. (2003) Targeted inactivation of dystrophin gene product Dp71: phenotypic impact in mouse retina. Hum. Mol. Genet. 12, 1543–1554.
201 Claudepierre T., Rodius F., Frasson M., Fontaine V., Picaud S., Dreyfus H., Mornet D. and Rendon A. (1999) Differential distribution of dystrophins in rat retina. Invest. Ophthalmol. Vis. Sci. 40, 1520–1529.
202 Drenckhahn D., Holbach M., Ness W., Schmitz F. and Anderson, L. V. (1996) Dystrophin and the dystrophin-associated glycoprotein, β-dystroglycan, co-localize in photoreceptor synaptic complexes of the human retina. Neuroscience 73, 605–612.
203 Blank M., Koulen P. and Kroger S. (1997) Subcellular concentration of β-dystroglycan in photoreceptors and glial cells of the chick retina. J. Comp. Neurol. 389, 668–678.
204 Schmitz F. and Drenckhahn D. (1997) Localization of dystrophin and β-dystroglycan in bovine retinal photoreceptor processes extending into the postsynaptic dendritic complex. Histochem. Cell. Biol. 108, 249–255.
205 Ueda H., Kato Y., Baba T., Terada N., Fujii Y., Tsukahara S. and Ohno S. (1997) Immunocytochemical study of dystrophin localization in cone cells of mouse retinas. Invest. Ophthalmol. Vis. Sci. 38, 1627–1630.
206 Ueda H., Baba T., Terada N., Kato Y., Tsukahara S. and Ohno S. (1997) Dystrophin in rod spherules; submembranous dense regions facing bipolar cell processes. Histochem. Cell. Biol. 108, 243–248.
207 Koulen P., Blank M. and Kroger S. (1998) Differential distribution of β-dystroglycan in rabbit and rat retina. J. Neurosci. Res. 51, 735–747.
208 Connors, N. C. and Kofuji P. (2002) Dystrophin Dp71 is critical for the clustered localization of potassium channels in retinal glial cells. J. Neurosci. 22, 4321–4327.
209 Newman E. and Reichenbach A. (1996) The Muller cell: a functional element of the retina. Trends Neurosci. 19, 307–312.
210 Nagelhus, E. A., Veruki, M. L., Torp R., Haug, F. M., Laake, J. H., Nielsen S., Agre P. and Ottersen, O. P. (1998) Aquaporin-4 water channel protein in the rat retina and optic nerve: polarized expression in Müller cells and fibrous astrocytes. J. Neurosci. 18, 2506–2519.
211 Nagelhus, E. A., Horio Y., Inanobe A., Fujita A., Haug, F. M., Nielsen S., Kurachi Y. and Ottersen, O. P. (1999) Immunogold evidence suggests that coupling of K^+ siphoning and water transport in rat retinal Müller cells is mediated by a coenrichment of Kir4.1 and AQP4 in specific membrane domains. Glia 26, 47–54.
212 Puwarawuttipanit W., Bragg, A. D., Frydenlund, D. S., Mylonakou, M. N., Nagelhus, E. A., Peters, M. F., Kotchabhakdi N., Adams, M. E., Froehner, S. C., Haug, F. M., Ottersen, O. P. and Amiry-Moghaddam M. (2006) Differential effect of alpha-syntrophin knockout on aquaporin-4 and Kir4.1 expression in retinal macroglial cells in mice. Neuroscience 137, 165–175.
213 Noel G., Belda M., Guadagno E., Micoud J., Klocker N. and Moukhles H. (2005) Dystroglycan and Kir4.1 coclustering in retinal Muller glia is regulated by laminin-1 and requires the PDZ-ligand domain of Kir4.1. J. Neurochem. 94, 691–702.
214 Araki E., Nakamura K., Nakao K., Kameya S., Kobayashi O., Nonaka I., Kobayashi T. and Katsuki M. (1997) Targeted disruption of exon 52 in the mouse dystrophin gene induced muscle degeneration similar to that observed in Duchenne muscular dystrophy. Biochem. Biophys. Res. Commun. 238, 492–497.
215 Kameya S., Araki E., Katsuki M., Mizota A., Adachi E., Nakahara K., Nonaka I., Sakuragi S., Takeda S. and Nabeshima Y. (1997) Dp260 disrupted mice revealed prolonged implicit time of the b-wave in ERG and loss of accumulation of β-dystroglycan in the outer plexiform layer of the retina. Hum. Mol. Genet. 6, 2195–2203.
216 Cibis, G. W., Fitzgerald, K. M., Harris, D. J., Rothberg, P. G. and Rupani M. (1993) The effects of dystrophin gene mutations on the ERG in mice and humans. Invest. Ophthalmol. Vis. Sci. 34, 3646–3652.
217 Pillers, D. M., Bulman, D. E., Weleber, R. G., Sigesmund, D. A., Musarella, M. A., Powell, B. R., Murphey, W. H., Westall C., Panton C., Becker, L. E., Worton, R. G. and Ray, P. N. (1993) Dystrophin expression in the human retina is required for normal function as defined by electroretinography. Nat. Genet. 4, 82–86.
218 Fitzgerald, K. M., Cibis, G. W., Giambrone, S. A. and Harris, D. J. (1994) Retinal signal transmission in Duchenne muscular dystrophy: evidence for dysfunction in the photoreceptor/depolarizing bipolar cell pathway. J. Clin. Invest. 93, 2425–2430.
219 D'Souza, V. N., Nguyen, T. M., Morris, G. E., Karges W., Pillers, D. A. and Ray, P. N. (1995) A novel dystrophin isoform is required for normal retinal electrophysiology. Hum. Mol. Genet. 4, 837–842.
220 Pillers, D. A., Fitzgerald, K. M., Duncan, N. M., Rash, S. M., White, R. A., Dwinnell, S. J., Powell, B. R., Schnur, R. E., Ray, P. N., Cibis, G. W. and Weleber, R. G. (1999) Duchenne/Becker muscular dystrophy: correlation of phenotype by electroretinography with sites of dystrophin mutations. Hum. Genet. 105, 2–9.
221 Green, D. G., Guo H. and Pillers, D. A. (2004) Normal photoresponses and altered b-wave responses to APB in the mdx(Cv3) mouse isolated retina ERG supports role for dystrophin in synaptic transmission. Vis. Neurosci. 21, 739–747.
222 Lee Y., Kameya S., Cox, G. A., Hsu J., Hicks W., Maddatu, T. P., Smith, R. S., Naggert, J. K., Peachey, N. S. and Nishina, P. M. (2005) Ocular abnormalities in Large(myd) and

Large(vls) mice, spontaneous models for muscle, eye, and brain diseases. Mol. Cell. Neurosci. 30, 160–172.
223 Lidov, H. G. and Kunkel, L. M. (1998) Dystrophin and Dp140 in the adult rodent kidney. Lab. Invest. 78, 1543–1551.
224 Tokarz, S. A., Duncan, N. M., Rash, S. M., Sadeghi A., Dewan, A. K. and Pillers, D. A. (1998) Redefinition of dystrophin isoform distribution in mouse tissue by RT-PCR implies role in nonmuscle manifestations of Duchenne muscular dystrophy. Mol. Genet. Metab. 65, 272–281.
225 Raats, C. J., van den Born J., Bakker, M. A., Oppers-Walgreen B., Pisa, B. J., Dijkman, H. B., Assmann, K. J. and Berden, J. H. (2000) Expression of agrin, dystroglycan, and utrophin in normal renal tissue and in experimental glomerulopathies. Am. J. Pathol. 156, 1749–1765.
226 Durbeej M., Jung D., Hjalt T., Campbell, K. P. and Ekblom P. (1997) Transient expression of Dp140, a product of the Duchenne muscular dystrophy locus, during kidney tubulogenesis. Dev. Biol. 181, 156–167.
227 Austin, R. C., Howard, P. L., D'Souza, V. N., Klamut, H. J. and Ray, P. N. (1995) Cloning and characterization of alternatively spliced isoforms of Dp71. Hum. Mol. Genet. 4, 1475–1483.
228 Lumeng, C. N., Hauser M., Brown V. and Chamberlain, J. S. (1999) Expression of the 71 kDa dystrophin isoform (Dp71) evaluated by gene targeting. Brain Res. 830, 174–178.
229 Rafael, J. A. and Brown, S. C. (2000) Dystrophin and utrophin: genetic analyses of their role in skeletal muscle. Microsc. Res. Tech. 48, 155–166.
230 Zuellig, R. A., Bornhauser, B. C., Knuesel I., Heller F., Fritschy, J. M. and Schaub, M. C. (2000) Identification and characterisation of transcript and protein of a new short N-terminal utrophin isoform. J. Cell. Biochem. 77, 418–431.
231 Kachinsky, A. M., Froehner, S. C. and Milgram, S. L. (1999) A PDZ-containing scaffold related to the dystrophin complex at the basolateral membrane of epithelial cells. J. Cell Biol. 145, 391–402.
232 McNeil, P. L. (1993) Cellular and molecular adaptations to injurious mechanical stress. Trends Cell Biol. 3, 302–307.
233 Fish, E. M. and Molitoris, B. A. (1994) Alterations in epithelial polarity and the pathogenesis of disease states. N. Engl. J. Med. 330, 1580–1588.
234 Fort P., Estrada, F. J., Bordais A., Mornet D., Sahel, J. A., Picaud S., Vargas, H. R., Coral-Vazquez, R. M. and Rendon A. (2005) The sarcoglycan-sarcospan complex localization in mouse retina is independent from dystrophins. Neurosci. Res. 53, 25–33.